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THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 12

JUNE 18, 1971

Synthetic Studies on Eritadenine. I.[1] Reactions of Some Purines with the 2,3-O-Protected Dihydroxybutyrolactone

KENTARO OKUMURA,* TOYONARI OINE, YOSHIHISA YAMADA, MASAYASU TOMIE, TAKESHI ADACHI, TAKEO NAGURA, MITSUTAKA KAWAZU, TOMISHIGE MIZOGUCHI, AND ICHIZO INOUE

Research Laboratory, Tanabe Seiyaku Co., Ltd., Kashima-cho, Higashiyodogawa-ku, Osaka, Japan

Received September 15, 1970

A convenient method for the synthesis of eritadenine (**8**) has been achieved *via* condensation of 2(*R*),3(*R*)-O-protected dihydroxybutyrolactone with the sodium salt of some purines: adenine (**1a**), 6-benzylamino- (**1b**), 6-(*N*,*N*-dimethylaminomethyleneamino)- (**1c**), 6-amino-8-methylthio- (**1d**), 6-amino-2-methylthio- (**1e**), and 6-methylthiopurine (**1f**). Reaction of 2(*R*),3(*R*)-cyclohexylidenedioxybutyrolactone (**2**) with the sodium salt of **1a** gave 4-(6-amino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**3a**) in fairly good yield along with small amount of 4-(6-amino-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**4a**). Similarly, the purines, **1b** and **1e**, afforded a predominant yield of 9-substituted purine and a lesser amount of 3-substituted purine; however, the purine **1d** gave both substituted purines in the ratio of 1:1. The purines, **1c** and **1f**, yielded 9-substituted and 7-substituted purine; in the case of **1c** the 7-substituted product was a major product, and it turned out to be a minor product in the case of **1f**. Each product obtained in the reaction was converted into the corresponding isomeric eritadenine, **8**, **9**, and **10**, by reduction or reductive desulfurization or amminolysis, and by subsequent hydrolysis. Reactivity of the lactones, 2(*R*),3(*R*)-cyclohexylidenedioxy- (**2**), 2(*R*),3(*R*)-isopropylidenedioxy- (**6**), and 2(*R*),3(*R*)-cyclopentylidenedioxybutyrolactone (**7**), was also investigated. This study suggested that the lactone **7** has the highest reactivity among others.

Recently we have reported[2] the structure and hypocholesterolemic activity of eritadenine (**8**) isolated from *Lentinus edodes* Sing. Kamiya[3] and coworkers have also reported their work on this substance. In view of the utility of eritadenine (**8**) as a new hypolipidemic agent, it became necessary for us to search for the convenient method of preparation. The usual construction[4] of the 9-substituted adenine by the stepwise synthesis starting from the pyrimidine or imidazole derivatives seemed to be circuitous for present purpose. Therefore, direct alkylation at N^9 of adenine (**1a**) with the reagent that has the requisite functional groups was first attempted. It is well known that a reaction[5] of γ-butyrolactone with potassium phthalimide affords 4-phthalimidobutyric acid in fairly good yield. The fact that the cleavage of the CH_2–O bond of the γ-butyrolactone and simultaneous formation of the CH_2–N bond had occurred in the course of this reaction prompted us to investigate the alkylation of adenine (**1a**) with the 2,3-O-protected dihydroxybutyrolactone in the presence of base.[6]

A reaction of 2(*R*),3(*R*)-cyclohexylidenedioxybutyrolactone (**2**) with the sodium salt of adenine (**1a**) at 140–145° in dimethylformamide afforded two isomeric products: A, mp 231–232° dec, and B, mp 280–282° dec. Elementary analysis of the products showed that they have the same empirical formula, $C_{15}H_{19}N_5O_4$, indicating them to be the 1:1 adduct of adenine (**1a**) and the lactone **2** (Scheme I).

The presence of the carboxyl group in the molecule, which was proved by the fact that they are soluble in aqueous sodium bicarbonate solution and regenerated upon acidification of the resulting solution, eliminated the occurrence of amide bond formation in the reaction. The major product A exhibits absorption at 259.5 nm (ε 15,300, pH 1.3) and 262 nm (ε 15,700, pH 12.5) and was converted into eritadenine (**8**) by acidic hydrolysis. These data confirm the structure of A as 4-(6-amino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**3a**). On the other hand, the structure of the minor product B was elucidated as 4-(6-amino-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**4a**) by the comparison of its ultraviolet spectrum [maximum at 276.5 nm (ε 18,800, pH 1.3), 276 nm (ε 12,600, pH 12.5), and difference (−4 nm) of the mini-

(1) Preliminary communication, *Chem. Commun.*, 1045 (1970).

(2) I. Chibata, K. Okumura, S. Takeyama, and K. Kotera, *Experientia*, **25**, 1237 (1969).

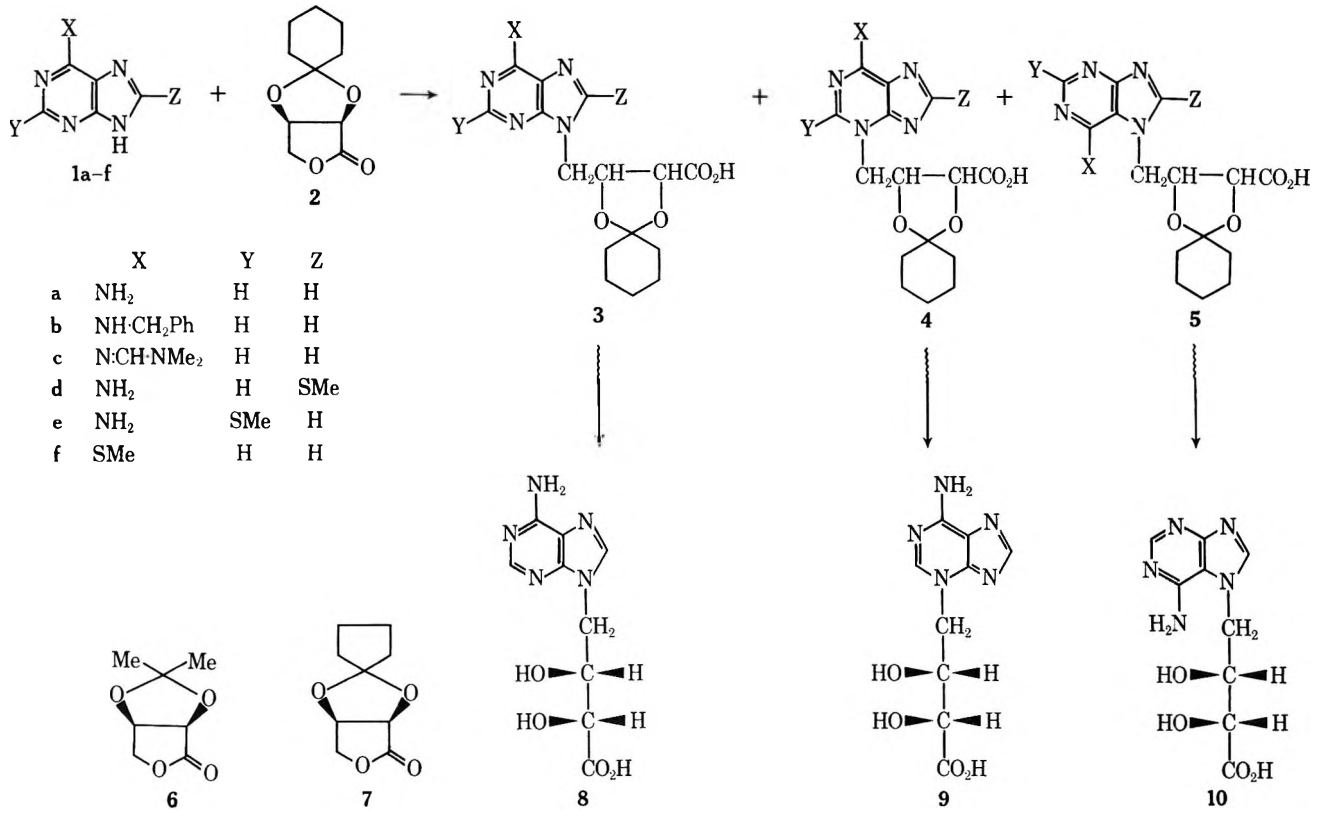
(3) (a) T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Tetrahedron Lett.*, 4729 (1969); (b) M. Hashimoto, Y. Saito, H. Seki, and T. Kamiya, *ibid.*, 1359 (1970); (c) T. Rokujo, H. Kikuchi, A. Tensho, Y. Tsukitani, T. Takenawa, K. Yoshida, and T. Kamiya, *Life Sci. (Oxford)*, **9**, 379 (1970).

(4) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press, London and New York, 1962, pp 61–68.

(5) G. Talbot, R. Gaudry, and L. Berlinguet, *Can. J. Chem.*, **36**, 593 (1958).

(6) While the author was preparing this manuscript, the similar investigation had been reported: T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Chem. Ind. (London)*, 652 (1970).

SCHEME I



mum from pH 1.0 to 7.0] and by the comparison of the $\Delta\delta$ value between the 2 and 8 protons in nmr spectrum (see Table IV) with those of 3-alkyladenines.[7] Acid hydrolysis of the crude mixture that was obtained by the reaction described above afforded a mixture of eritadenine (**8**) and 3-isoeritadenine (**9**), 4-(6-amino-3*H*-purin-3-yl)-2(*R*),3(*R*)-dihydroxybutric acid, in good yield. Chromatographic analysis by ion-exchange resin showed the ratio of the 9:3 isomer (**8**:**9**) to be approximately 10:1 and the absence of the other isomer. In an effort to improve the yield of this reaction, experiments were carried out under various conditions, change of solvent, base, and temperature, but gave no significant result. However, with the expectation that the alteration of alkylidene moiety of the ketal ring in the lactone might give preferable influence on the yield of the reaction, the lactones, 2(*R*),3(*R*)-isopropylidenedioxy- (**6**),[8] 2(*R*),3(*R*)-cyclopentylidenedioxy- (**7**), and 2(*R*),3(*R*)-cyclohexylidenedioxybutyrolactone (**2**), were subjected to the reaction at lower temperature (100°) at which the decomposition of the lactones would not affect evaluation of the relative reactivities. The higher reactivity of the lactone **7** can be deduced from the data described in Table I, and this would be explained by an assumption that the cyclopentylidene moiety would exert its higher strain on the lactone ring to make the γ carbon of the lactone more susceptible to the nucleophile.

However, at higher temperatures (140–145°), the lactones **2** and **6** gave better results than the lactone **7**.

(7) (a) N. J. Leonard and J. A. Deyrup, *J. Amer. Chem. Soc.*, **84**, 2148 (1962); (b) B. C. Pal, *Biochemistry*, **1**, 558 (1962); (c) N. J. Leonard and R. A. Laursen, *J. Amer. Chem. Soc.*, **85**, 2026 (1963); (d) J. A. Montgomery and H. J. Thomas, *J. Heterocycl. Chem.*, **1**, 115 (1964); (e) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Amer. Chem. Soc.*, **86**, 5320 (1964).

(8) D. L. Mitchell, *Can. J. Chem.*, **41**, 214 (1963).

TABLE I

COMPARISON OF THE YIELDS OF THE ERITADENINE (**8**) IN THE REACTION OF THE LACTONES WITH THE SODIUM SALT OF ADENINE

No.	Lactone	Reaction temp, °C	Time, hr	Yield[a] of eritadenine, % Analyzed[b]	Isolated
1	6	100	50	20	10
2	2	100	50	22	12
3	7	100	50	37	24.5

[a] Approximately 10% of 3-isoeritadenine (**9**) is contaminated. [b] An aliquot of the acid hydrolysate of the concentrated reaction mixture, after neutralization, was submitted to paper partition chromatography [Toyo No. 51A filter paper, solvent system 1-butanol-AcOH-H_2O (18:8:5), by the ascending method]. Eritadenine, which is visualized on the developed chromatogram under uv light, was extracted with Clark-Lubs buffer solution (pH 1.4) and determined by means of uv spectrometry.

This inconsistency would be due to the lower stability of the lactone **7**.

Then, the investigation was extended to the reactions of the lactone **2** with other substituted purines **1b–f** that would be convertible into adenine. The reactions were carried out under similar conditions to that described for adenine (**1a**), and thus isomerically substituted products were obtained in the varying ratio which depends on the directive influence of the substituent on the purine ring (Table II).

The attaching sites of the side chain of the products were established by an analogy of uv spectra (Table III) with those of suitable model compounds reported in the literature and confirmed by conversion of the intermediates into the isomeric eritadenine, **8**, **9**, and **10**, respectively.

The previous proposal[7e] for differentiating N^3-substituted adenine between isomerically substituted adenines by nmr spectra and melting points holds also for the sets of our products (see Table IV).

TABLE II

PRODUCT COMPOSITION IN THE REACTIONS OF THE PURINES (1a–f) WITH THE LACTONE (2)

Expt no.	Purine	Product ratio 9 isomer	3 isomer	7 isomer	Total yield, %
1	1a	100	9[a]		44.2
2	1b	100	34		31.2
3	1c	100[b]	Trace[d]	184	36.5
4	1d	100	103[c]		26.8
5	1e	100	Trace[a]		52.0
6	1f	100[c]		9	67.3

[a] Determined by uv spectrometric analysis of the mixture obtained from the hydrolysate of the crude product. [b] As the intermediate 3c could not be isolated owing to the instability of the N^6-protecting group, the value was estimated from the amount of the final product 8. [c] Determined by nmr spectrometric analysis of the mixture. [d] Determined by paper electrophoresis of the mixture.

TABLE III

ULTRAVIOLET ABSORPTION DATA OF ISOMERICALLY SUBSTITUTED PURINES

Compd	pH 1.3 Max, nm	pH 1.3 $\epsilon \times 10^{-3}$	pH 7 Max, nm	pH 7 $\epsilon \times 10^{-3}$	pH 12.5 Max, nm	pH 12.5 $\epsilon \times 10^{-3}$	Ref[a]
3a	259.5	15.3	262	15.7	262	15.7	2
4a	276.5	18.8	276	14.1	276	12.6	7a–d
3b	268.5	21.8	271.5	21.8	271.5	22.0	17
4b	288	23.3	291	17.8	292	17.1	17
3d	286	22.0	280.5	21.6	280.5	19.6	*b*
4d	303	25.8	308	19.3	308	25.8	
3e	271.5	17.1	277.5	15.2	277.5	15.2	*c*
5a	275	13.6	272.5	9.8	272.5	9.8	7a, *d*
3f	286	Sh[e]	286	21.0	286	21.2	*f, g*
	294	19.3	294	21.0	294	21.0	
5f	303	12.4	295	13.8	295	13.8	*g, h*
	296	Sh	302	Sh	302	Sh	

[a] The spectral data of the model compounds shown in these references were compared with those of the compounds listed in Table III. [b] R. E. Holmes and R. K. Robins, *J. Amer. Chem. Soc.*, 86, 1242 (1964). [c] Y. Ishido, T. Sato, and Y. Kikuchi, *Nippon Kagaku Zasshi*, 86, 240 (1965); H. J. Schaeffer and H. J. Thomas, *J. Amer. Chem. Soc.*, 80, 3738 (1958). [d] J. A. Montgomery and H. J. Thomas, *ibid.*, 85, 2672 (1963). [e] Sh = shoulder. [f] D. E. O'Brien, J. D. Westover, R. K. Robins, and C. C. Cheng, *J. Med. Chem.*, 8, 182 (1965). [g] Z. Neiman and F. Bergmann, *Israel J. Chem.*, 3, 161 (1965); B. Pullman, H. Berthod, F. Bergmann, Z. Neiman, H. Weiler-Feilchenfeld, and E. D. Bergmann, *Tetrahedron*, 26, 1483 (1970). [h] R. J. Rousseau, R. P. Panzica, S. M. Reddick, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, 35, 631 (1970).

TABLE IV

MELTING POINTS AND DIFFERENCES OF THE CHEMICAL SHIFT (IN D_2O–NaOD)[a] BETWEEN THE SIGNALS OBSERVED FOR THE 2- AND 8-AROMATIC PROTONS OF THE COMPOUNDS

Compd	Mp, °C, dec	Δδ, cps	Compd	Mp, °C, dec	Δδ, cps
8	261–263	3	3a	231–232	7[b]
9	297–299	30	4a	280–282	15
10	278–279	5	5a	242–244	2

[a] Solute concentration is about 0.2 mol. [b] Determined in DMSO-d_6.

In the case of N^6-benzyladenine[9] (**1b**), the 9 isomer **3b** [4-(6-benzylamino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid] was a major product, though the relative yield of the 3 isomer **4b** [4-(6-benzylamino-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid] increased slightly. Mild hydrolysis (at 80–90°, 1 hr) of **3b** and **4b** with dilute hydrochloric acid gave N^6-benzyleritadenine (**11**) and N^6-benzyl-3-isoeritadenine (**12**), respectively, in good yield. Both **11** and **12** resisted stubbornly hydrogenolytic debenzylation. However, reductive debenzylation of **11** with sodium in liquid ammonia yielded **8** in low yield (13.7%).

The *N*,*N*-dimethylaminomethylene group had been widely used[10] in the chemistry of nucleotides to protect the reactive amino functions of heterocyclic moieties. However, the alkylation of 6-(*N*,*N*-dimethylaminomethyleneamino)purine (**1c**) has not been attempted up to the present. Therefore, it was interesting for us to study the directive influence of the *N*,*N*-dimethylaminomethyleneamino group on the purine in our alkylation reaction.

Interestingly, the 7 isomer **5c** {4-[6-(*N*,*N*-dimethylaminomethyleneamino)-7*H*-purin-7-yl]-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid}, maximum at 332 nm (ϵ 38,100, pH 1.3) and 316 nm (ϵ 28,100, at pH 12.5), was obtained predominantly, and the 9 isomer **3a**, which would arise from the intermediary product **3c** by deblocking of the protective group in the course of separation, was also obtained as the second product. Chromatographic analysis of the partially purified mixture that was obtained from the acid hydrolysate of the reaction product showed the presence of a minute amount of **9**. However, this does not necessarily indicate the occurrence of the alkylation at N^3 of **1c**, because the partial decomposition, though very small, of **1c** into adenine under the reaction condition was observed in a preliminary experiment by which the stability of **1c** was checked, and the resultant adenine would react with the lactone **2**, yielding **3a** and **4a**. Treatment of **5c** with 5% ammonium hydroxide caused hydrolysis of the N^6-protective group selectively to give 4-(6-amino-7*H*-purin-7-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**5a**), which on acid hydrolysis afforded the 7-isoeritadenine (**10**) [4-(6-amino-7*H*-purin-7-yl)-2(*R*),3(*R*)-dihydroxybutyric acid]. The structure of 7-isoeritadenine (**10**) was assigned by the elemental analysis and ultraviolet spectra [maximum at 275 nm (ϵ 14,100, pH 1.3), 272.5 nm (ϵ 10,400, pH 12.5) and difference (+7 nm) of the minimum from pH 1.0 to 7.0] and finally confirmed by the direct comparison of its spectrometric data with those of authentic sample that was prepared unambiguously *via* methyl 5-(5′-amino-4′-cyanoimidazol-3′-yl)-2,3-*O*-isopropylidene ribofuranoside.[11]

The alkylation of the sodium salt of 6-amino-8-methylthiopurine (**1d**)[12] with the lactone **2** gave a mixture of the 9 isomer **3d** [4-(6-amino-8-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid] and the 3 isomer **4d** [4-(6-amino-8-methylthio-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid]. Both isomers were obtained pure by chromatographic separation with silica gel in the ratio of approximately 1:1. The ratio was supported by the integration of each ring proton signal (δ 8.13 ppm of **3d** and 8.25 ppm of **4d**) in the nuclear magnetic resonance (nmr) spectrum of the mixture.

(9) C. W. Whitehead and J. J. Travrso, *J. Amer. Chem. Soc.*, 82, 3973 (1960).

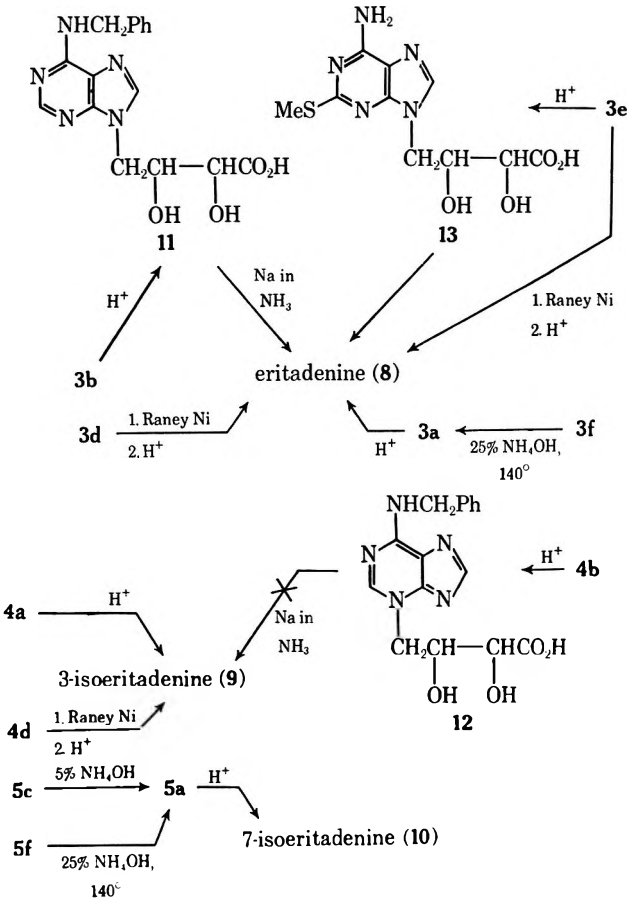
(10) A. Holy and J. Zemlicka, *Collect. Czech. Chem. Commun.*, 34, 2449 (1969), and references therein.

(11) S. Ohoshiro, T. Nagura, and K. Okumura, unpublished work.

(12) R. K. Robins, *J. Amer. Chem. Soc.*, 80, 6671 (1958).

Desulfurization of **3d** and **4d** with Raney nickel, after acid hydrolysis, afforded the isomeric eritadenine, **8** and **9**, respectively (Scheme II).

SCHEME II



In the case of 6-amino-2-methylthiopurine (**1e**),[13] the 9 isomer **3e** [4-(6-amino-2-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid] was again a major product, and concomitant yield of the 3 isomer **4e** [4-(6-amino-2-methylthio-3*H*-purin-3-yl)-2-(*R*),3(*R*)-cyclohexylidenedioxybutyric acid] diminished so markedly that the formation of **4e** was detected only by chromatographic analysis of the product which was obtained after desulfurization and acid hydrolysis of the crude reaction product. The high yield of **4d** from **1d** and the extremely low yield of **4e** from **1e** are attributable to steric hindrance by the methylthio groups at C_2 or C_8 of the purine (**1d** or **1e**).

The alkylation of the sodium salt of 6-methylthiopurine (**1f**)[14] with the lactone **2** gave the 9 isomer **3f** [4-(6-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid] in fairly good yield along with small amounts of the 7 isomer **5f** [4-(6-methylthio-7*H*-purin-7-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid] which was isolated by chromatographic separation with silica gel. Ammonolysis of **3f** and **5f** with 25% ammonium hydroxide at 140–145° yielded **3a** and **5a**, respectively.

Some of the reactions described here provide a convenient method for the preparation of eritadenine because of simplicity of the reaction and availability of the material used.

(13) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Amer. Chem. Soc.*, **81**, 2442 (1959).

(14) G. B. Eliton, E. Burgi, and G. H. Hitchings, *ibid.*, **74**, 411 (1952).

Experimental Section

Melting points were determined on a Yamato apparatus MP-21 and are uncorrected. The nmr spectra were determined on a Hitachi Perkin-Elmer R-20A instrument with tetramethylsilane as internal standard. Uv spectra were determined on a Hitachi EPS-2U instrument.

2(*R*),3(*R*)-Cyclohexylidenedioxybutyrolactone (2).—A mixture of 2(*R*),3(*R*)-dihydroxybutyrolactone[15] (59 g), cyclohexanone (50 g), *p*-toluenesulfonic acid (2.5 g), and benzene (350 ml) in a flask equipped with Dean-Stark separator was refluxed for 5 hr (the water that had formed was removed from the separator). The mixture was diluted with 150 ml of benzene and cooled; then the diluted mixture was washed with H_2O, saturated aqueous sodium bicarbonate solution, and again with H_2O. The benzene layer was dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The residue was triturated with 100 ml of hexane and collected by filtration to give **2**, yield 93 g (90%). Recrystallization from cyclohexane gave analytically pure **2** as colorless leaflets: mp 76–78°; $[\alpha]^{20}D$ −104° (*c* 1.0, $CHCl_3$); ir (Nujol) 1764 cm^{-1} ($\nu_{C=O}$).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.51; H, 7.03.

2(*R*),3(*R*)-Cyclopentylidenedioxybutyrolactone (7).—A mixture of 2(*R*),3(*R*)-dihydroxybutyrolactone (59 g), cyclopentanone (44 g), *p*-toluenesulfonic acid (5 g), and benzene (500 ml) was refluxed for 7 hr. Similar treatment to that described above gave **7**, yield 67 g (69.5%). Recrystallization from isopropyl ether gave analytically pure **7** as colorless prisms: mp 47–49°; $[\alpha]^{20}D$ −107.2° (*c* 1.0, $CHCl_3$); ir (Nujol) 1773 cm^{-1} ($\nu_{C=O}$).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.54; H, 6.37.

6-(*N*,*N*-Dimethylaminomethyleneamino)purine (1c).—A mixture of adenine (**1a**, 91 g, 0.67 mol), DMF (1680 ml), and dimethylformamide dimethyl acetal[16] (101 g) was stirred at 50° for 6 hr. The mixture was evaporated to dryness *in vacuo* and the residue was triturated with EtOH. The resulting crystals were filtered and dried. Recrystallization from a 1:1 mixture of DMF and EtOH gave **1c**: yield 109.5 g (86.2%); mp 252–255°; nmr (DMSO-d_6) δ 3.36 (s, 3 H), 3.42 (s, 3 H), 8.61 (s, 1 H), 8.73 (s, 1 H), 9.19 (s, 1 H); uv max ($\epsilon \times 10^{-3}$) 222.5 nm (16.0), 287 (13.1), and 324 (21.7) at pH 1.6, 225 (14.4) and 310 (33.8) at pH 7.0, 227 (15.9) and 308 (23.9) at pH 12.6.

Anal. Calcd for $C_8H_{10}N_6$: C, 50.51; H, 5.30; N, 44.19. Found: C, 50.41; H, 5.19; N, 44.41.

General Procedure for the Reactions of the Sodium Salts of the Purines (1a–f) with 2(*R*),3(*R*)-Cyclohexylidenedioxybutyrolactone (2).—The sodium salt of the purine was prepared by stirring a suspension of an equimolar amount of the purine and sodium hydride (in mineral oil) in DMF (4 ml/mmol of the purine) at 100° for 1 hr. To this suspension was added the lactone **2** (equimolar amount) and stirring was continued at 140–145° for 15 hr. After cooling, the insoluble solid that had formed was filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was treated in the appropriate manner for the respective reaction.

This procedure was employed for the reaction, unless otherwise stated.

Reaction of the Sodium Salt of Adenine (1a).—A mixture of the sodium salt of adenine (**1a**, 50 mmol), the lactone **2** (6.0 g, 50 mmol), and DMF (200 ml) was treated in the manner described in the general procedure. The resulting residue was dissolved in 50 ml of H_2O, and the solution was treated with charcoal and filtered. The filtrate was passed through a column of Amberlite IRC-50 (H form, 80 ml) and the column was washed with 1 l. of H_2O. The eluate and washing was evaporated to dryness *in vacuo*. The residue was dissolved in H_2O (30 ml) and the solution was acidified to pH 3.0 with 2% formic acid. The crude product that had precipitated was collected by filtration. The crude product was dissolved in H_2O (30 ml) containing 2 g of $NaHCO_3$, and the solution was treated with charcoal and filtered. The filtrate was acidified to pH 3.5 with formic acid and the precipitate that had formed was collected by filtration to yield 5.9 g of an approximately 10:1 mixture of 4-(6-amino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**3a**) and 4-(6-

(15) (a) A. Jeanes and C. S. Hudson, *J. Org. Chem.*, **20**, 1565 (1955); (b) A. S. Perlin and C. Brice, *Can. J. Chem.*, **33**, 1216 (1955); (c) R. Barker and D. L. MacDonald, *J. Amer. Chem. Soc.*, **82**, 2301 (1960).

(16) Z. Aronild and M. Kornilov, *Collect. Czech. Chem. Commun.*, **29**, 645 (1961).

amino-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**4a**). The mixture was suspended in 20 ml of DMF and the suspension was boiled for 10 min. Insoluble material was removed by filtration while still hot and the filtrate was cooled. The colorless prisms that had formed were collected by filtration to give **3a**, yield 5.0 g (35.4%), mp 227–229° dec. The analytical sample that was recrystallized from DMF melted at 231–232° dec: $[\alpha]^{25}D$ +97.8° (*c* 1.0, 0.1 *N* NaOH); nmr (DMSO-d_6) δ 1.1–1.9 (m, 10 H), 4.1–4.3 (m, 2 H), 4.6–4.9 (m, 2 H), 8.20 (s, 1 H), 8.27 (s, 1 H).

Anal. Calcd for $C_{15}H_{19}N_5O_4$: C, 54.04; H, 5.75; N, 21.01. Found: C, 53.93; H, 5.74; N, 20.90.

The solid that was insoluble in hot DMF was dissolved in 10 ml of 2% aqueous sodium bicarbonate solution. After filtration, the solution was acidified to pH 3.5 to yield crude **4a** (0.4 g) which was collected by filtration. A suspension of **4a** in 10 ml of DMF was boiled for 5 min and the insoluble solid was collected by filtration while hot. This solid was dissolved again in 8 ml of 2% aqueous sodium bicarbonate solution and the solution was acidified to pH 3.5 to give pure **4a**, yield 370 mg (2.6%). The analytical sample was dried at 110° over P_2O_5 for 40 hr *in vacuo:* mp 280–282° dec; $[\alpha]^{25}D$ +145.6° (c 1.0, 0.1 *N* NaOH); nmr (D_2O–NaOD) δ (dioxane as internal reference) 0.8–1.9 (m, 10 H), 3.9–4.9 (m, 4 H), 7.77 (s, 1 H), 8.0 (s, 1 H).

Anal. Calcd for $C_{15}H_{19}N_5O_4$: C, 54.04; H, 5.75; N, 21.01. Found: C, 54.14; H, 5.70; N, 20.87.

Direct isolation of eritadenine (**8**) and 3-isoeritadenine (**9**) from the acid hydrolysate of the crude reaction product was carried out in the following manner.

The reaction of the sodium salt of adenine (**1a**, 8.1 g, 60 mmol) with the lactone **2** (9.9 g, 50 mmol) was carried out in the manner described in the general procedure. The resulting residue was dissolved in 10% hydrochloric acid (50 ml) and the solution was heated at 80° for 1 hr. After cooling, the solution was treated with charcoal and filtered. The filtrate was diluted with H_2O (40 ml) and neutralized with 25% ammonium hydroxide. To this solution was added 3.5 g of $MgCl_2 \cdot 6H_2O$, and the mixture was allowed to stand at room temperature overnight. A mixture (8.0 g) of the magnesium salt of eritadenine (**8**) and 3-isoeritadenine (**9**) that had separated was collected by filtration. The mixture of the magnesium salts was dissolved in dilute hydrochloric acid and the solution was treated with charcoal and then filtered. The filtrate was adjusted to pH 3.0 with 10% aqueous sodium hydroxide to give a mixture (5.0 g, 39%) of **8** and **9**; the mixture was shown to be a 100:8 mixture of **8** and **9** by ultraviolet spectral analysis. The mixture (5.0 g) was dissolved in H_2O (35 ml) containing $NaHCO_3$ (1.7 g) with slight warming. The solution was treated with charcoal and filtered. To the hot filtrate was added 170 ml of boiling ethanol. The mixture was allowed to stand at room temperature overnight and the resulting crystals of the sodium salt of **8** were collected by filtration. Further crystallization from 80% EtOH gave the pure sodium salt of **8** as colorless leaflets: yield 5.1 g; mp 265–266° dec; $[\alpha]^{25}D$ +39.4° (*c* 2.0, H_2O). The analytical sample was dried at 50° for 7 hr.

Anal. Calcd for $C_9H_{10}N_5O_4Na \cdot 2^1/_2H_2O$: C, 33.75; H, 4.72; N, 21.87. Found: C, 33.99; H, 4.73; N, 21.74.

From the sodium salt, pure eritadenine (**8**) was obtained, mp 265–266° dec.

Anal. Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.67. Found: C, 42.78; H, 4.52; N, 27.78.

This product was identical in all respects, decomposition point, uv and ir spectra, behavior on paper electrophoresis, and specific rotation, with natural eritadenine (**8**).

The mother liquors from the purification of the sodium salt were combined and evaporated to dryness *in vacuo*. The residue was recrystallized twice from 70% EtOH to give the sodium salt of 3-isoeritadenine (**9**, 0.2 g) as colorless prisms, mp 281–282° dec.

This sodium salt was dissolved in H_2O (2 ml), and the solution was acidified to pH 4 with 2% formic acid to give pure **9**.

Recrystallization from H_2O gave the analytically pure sample as colorless prisms: mp 297–299° dec; $[\alpha]^{25}D$ +86.7° (c 1.0, 0.1 *N* NaOH); uv max ($\epsilon \times 10^{-3}$) 276 nm (19.7) at pH 1.3, 276 (15.4) at pH 7, 276 (14.0) at pH 12.5; nmr (D_2O–NaOD) δ 4.2–4.6 (m, 4 H), 7.90 (s, 1 H), 8.20 (s, 1 H).

Anal. Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.67. Found: C, 42.81; H, 4.38; N, 27.45.

Reaction of the Sodium Salt of 6-Benzylaminopurine (1b).—A mixture of the sodium salt of **1b** (0.25 mol), the lactone **2** (49.5 g, 0.25 mol), and DMF (1250 ml) was treated in the manner described in the general procedure. The resulting residue was added to 750 ml of 5% aqueous sodium bicarbonate solution and the insoluble solid, which was found to be unchanged **1b** (21.6 g, recovery of 38.4%), was collected by filtration. The filtrate was acidified to pH 3 with 300 ml of 10% formic acid and the crystals that had precipitated were collected by filtration. These crystals were dissolved in EtOH (1000 ml), and the solution was allowed to stand at room temperature overnight. The deposited crystals were collected by filtration and dried to give a crude sample of 4-(6-benzylamino-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**4b**), yield 8.4 g (7.9%), mp 226–229°. Recrystallization from DMF afforded the analytically pure sample as colorless prisms, mp 260–261° dec, $[\alpha]^{25}D$ +87.1° (*c* 1.0, 0.1 *N* NaOH).

Anal. Calcd for $C_{22}H_{25}N_5O_4$: C, 62.40; H, 5.95; N, 16.54. Found: C, 62.64; H, 6.07; N, 16.76.

The ethanol filtrate was evaporated to dryness *in vacuo* and the residue was crystallized from a smaller amount of EtOH to give 4-(6-benzylamino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**3b**), yield 24.7 g (23.3%), mp 187–189° dec. Recrystallization from MeOH afforded the analytically pure sample as colorless leaflets; mp 187–189° dec; $[\alpha]^{25}D$ +71.8° (*c* 1.0, 0.1 *N* NaOH); nmr (DMSO-d_6) δ 1.10–2.10 (m, 10 H), 4.30 (m, 2 H), 4.85 (m, 4 H), 7.31 (m, 5 H), 8.12 (s, 1 H), 8.23 (s, 1 H), 8.28 (m, 1 H).

Anal. Calcd for $C_{22}H_{25}N_5O_4$: C, 62.40; H, 5.95; N, 16.54. Found: C, 62.36; H, 5.92; N, 16.68.

Reaction of the Sodium Salt of 6-(*N*,*N*-Dimethylaminomethyleneamino)purine (1c).—A mixture of the sodium salt of **1c** (0.15 mol), the lactone **2** (29.7 g, 0.15 mol), and DMF (1000 ml) was treated in the manner described in the general procedure. (In this experiment, the reaction was carried out at 120° for 12 hr.)

The resulting residue was triturated with ether and the insoluble solids were collected by filtration and redissolved in MeOH. The methanol solution was passed through a column of Amberlite IRC-50 (H form, 500 ml, in MeOH). The eluate and methanolic washing (total volume, 2.4 l.) was evaporated to dryness *in vacuo*, and to the residue was added 500 ml of H_2O. The insoluble solid, which was found to be unchanged starting material **1c**, was removed by filtration, recovery 9.4 g (31.6%), mp 82–84°. Magnesium chloride hexahydrate (70 g) was added to the filtrate and the solid that had formed was collected by filtration to give the magnesium salt of 4-[6-(*N*,*N*-dimethylaminomethyleneamino)-7*H*-purin-7-yl]-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**5c**). The magnesium salt was dissolved in dilute hydrochloric acid and the pH of the solution was adjusted to 3.5 with 10% sodium hydroxide solution. The crystals that had precipitated were collected by filtration and dried to give crude **5c** (22 g, mp 205–208° dec). Recrystallization from EtOH gave pure **5c** as colorless needles: yield 13.8 g (23.7%); mp 211–213°; $[\alpha]^{25}D$ +150.5° (c 1.0, 0.1 *N* NaOH); mass spectrum M^+ 388; nmr (DMSO-d_6) δ 1.0–2.0 (m, 10 H), 3.05 (s, 3 H), 3.13 (s, 3 H), 4.55–5.05 (m, 4 H), 8.24 (s, 1 H), 8.39 (s, 1 H), 8.99 (s, 1 H); uv max ($\epsilon \times 10^{-3}$) 332 nm (38.1) at pH 1.3, 318 (28.1) at pH 7, 316 (28.1) at pH 12.5.

Anal. Calcd for $C_{18}H_{24}N_6O_4$: C, 55.66; H, 6.23; N, 21.64. Found: C, 56.10; H, 6.18; N, 21.71.

The mother liquor from filtration of the magnesium salt of **5c** was evaporated to dryness *in vacuo*. The residue was triturated with 2-propanol and the insoluble solid was collected by filtration. The solid was dissolved in dilute hydrochloric acid and the pH of the solution was adjusted to 3.5 with 10% sodium hydroxide solution. The precipitate that had formed was collected by filtration and dried to give 4-(6-amino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**3a**), yield 6.4 g (12.8%), mp 218–220° dec. This product was identical in its uv and ir spectra with those of the sample obtained in the case of adenine (**1a**).

Reaction of the Sodium Salt of 8-Methylthio-6-aminopurine (1d).—A mixture of the sodium salt of **1d** (30 mmol), the lactone **2** (6.0 g, 31 mmol), and DMF (100 ml) was treated in the manner described in the general procedure. The resulting residue was dissolved in 100 ml of H_2O, and the solution, after treatment with charcoal, was passed through a column of Amberlite IRC-50 (H form, 100 ml). The column was washed with H_2O, and the eluate and washing (total 1500 ml) was evaporated to dryness *in vacuo*. The residue was shown by tlc (on silica gel, solvent $CHCl_3$–MeOH–AcOH 85:15:3) to be a mixture of two major products. This was chromatographed on silica gel (0.2–0.5 mm, 150 g, solvent $CHCl_3$–MeOH–AcOH, 80:20:3).

By suitable combination of fractions (on the basis of their tlc characteristics), two pure components were obtained. The first fraction to be eluted from the column was dissolved in 15 ml of 5% aqueous sodium bicarbonate solution, and the solution was acidified to pH 3 with 10% formic acid. The crystals that had precipitated were collected by filtration and dried. Recrystallization of the crystals from 50% MeOH gave 4-(6-amino-8-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**3d**) as colorless prisms: yield 0.49 g (13.2%); mp 173–175° dec; $[\alpha]^{25}D$ +65.0° (*c* 1.0, 0.1 *N* NaOH); nmr (DMSO-d_6) δ 0.9–2.1 (m, 10 H), 2.73 (s, 3 H), 4.20 (m, 2 H), 4.62–5.10 (m, 2 H), 8.20 (s, 1 H).

Anal. Calcd for $C_{16}H_{21}N_5O_4S \cdot {}^1/_2H_2O$: C, 49.47; H, 5.71; N, 18.03; S, 8.25. Found: C, 49.82; H, 5.48; N, 17.80; S, 8.28.

The second component was recrystallized from 60% MeOH to give 4-(6-amino-8-methylthio-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**4d**) as colorless needles: yield 0.47 g (13.6%); mp 216–218° dec; $[\alpha]^{25}D$ +145° (*c*, 1.0, 0.1 *N* NaOH); nmr (DMSO-d_6) δ 1.05–2.0 (m, 10 H), 2.62 (s, 3 H), 3.95–4.60 (m, 2 H), 4.60–5.05 (m, 2 H), 8.22 (s, 1 H).

Anal. Calcd for $C_{16}H_{21}N_5O_4S \cdot H_2O$: C, 48.35; H, 5.83; N, 17.62. Found: C, 48.46; H, 5.58; N, 17.31.

Reaction of the Sodium Salt of 6-Amino-2-methylthiopurine (1e).—A mixture of the sodium salt of **1e** (26 mmol), the lactone **2** (8.6 g, 43 mmol), and DMF (150 ml) was treated in the manner described in the general procedure. The resulting residue was dissolved in H_2O and the insoluble solid, which was found to be unchanged **1e**, was filtered off. The filtrate was treated with charcoal and filtered.

This decolorized solution was acidified to pH 3 with 80% formic acid. The solid that had formed was collected by filtration, washed with H_2O, and dried. Recrystallization from acetone gave 4-(6-amino-2-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**3e**) as colorless granules: yield 5.2 g (52%); mp 172–173°; $[\alpha]^{20}D$ +84.8° (*c* 1.0, 0.1 *N* NaOH); nmr (DMF-d_7) δ 1.30–1.80 (m, 10 H), 2.52 (s, 3 H), 4.1–4.5 (m, 2 H), 4.85–5.0 (m, 2 H), 7.30 (s, 2 H), 8.08 (s, 1 H).

Anal. Calcd for $C_{16}H_{21}N_5O_4S$: C, 50.65; H, 5.58; N, 18.46. Found: C, 50.64; H, 5.44; N, 18.01.

In another run, 4-(6-amino-2-methylthio-9*H*-purin-9-yl)-2(*R*),-3(*R*)-dihydroxybutyric acid (**13**) was obtained directly by the following treatment described below. The resulting residue was treated with 10% hydrochloric acid at 80–85° for 30 min. This hydrolysate was evaporated to dryness *in vacuo*. The residue was dissolved in 30 ml of H_2O, and the solution was filtered with charcoal. After having been concentrated to one-third of its volume, the filtrate was adjusted to pH 8 with sodium bicarbonate and the unchanged material **1e** was recovered by filtration. The mother liquor was acidified to pH 3 with 80% formic acid at 60°. After cooling, the solid that had formed was collected by filtration and washed with H_2O. Recrystallization from H_2O afforded **13** as colorless fine needles: yield 3.6 g (47.4%); mp 242° dec; $[\alpha]^{20}D$ +52.0° (*c* 1.0, 0.1 *N* NaOH); nmr (DMF-d_7) δ 2.48 (s, 3 H), 3.9–4.25 (m, 4 H), 4.5–6.5 (broad, 2 H), 7.21 (s, 2 H), 7.9 (s, 1 H); uv max ($\epsilon \times 10^{-3}$) 271.5 nm (15.6) at pH 1.3, 235 (22.4), 278 (14.4) at pH 7, 235 (22.4), 278 (14.4) at pH 12.5.

Anal. Calcd for $C_{10}H_{13}N_5O_4S$: C, 40.13; H, 4.38; N, 23.40. Found: C, 40.15; H, 4.42; N, 23.09.

Reaction of the Sodium Salt of 6-Methylthiopurine (1f).—A mixture of the sodium salt of **1f** (50 mmol), the lactone **2** (9.9 g, 50 mmol), and DMF (200 ml) was treated in the manner described in the general procedure. The resulting residue was dissolved in 40 ml of H_2O, and the solution was filtered with charcoal. The filtrate was passed through a column of Amberlite IRC-50 (H form, 80 ml), and the column was washed with H_2O (700 ml). The eluate and washing was concentrated to a volume of 40 ml and acidified to pH 3. Crystals that had formed were collected by filtration, weighing 8.5 g; it decomposed at 162–167°. The crude product was dissolved in 80 ml of H_2O containing sodium bicarbonate (2 g). After treatment with charcoal, the solution was acidified to pH 3 and the precipitate that had separated was collected by filtration, yield 8.1 g, mp 165–168° dec. Recrystallization from 50% EtOH gave 4-(6-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**3f**) as colorless fine needles: mp 167–170° dec; $[\alpha]^{25}D$ +91.8° (*c* 1.0, 0.1 *N* NaOH); nmr ($CDCl_3$) δ 1.1–2.0 (m, 10 H), 2.64 (s, 3 H), 4.0–5.3 (m, 4 H), 8.23 (s, 1 H), 8.78 (s, 1 H).

The analytical sample was obtained by recrystallization from 50% EtOH, mp 170–172° dec.

Anal. Calcd for $C_{16}H_{20}N_4O_4S$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.60; H, 5.55; N, 15.27.

The combined acidic (pH 3.0) mother liquors were adjusted to pH 1.5 and the precipitate that had separated was collected by filtration. This solid (3.0 g) was dissolved in 3% aqueous sodium bicarbonate solution (30 ml), and the solution was acidified to pH 3.0. The additional fraction of **3f** (1.7 g), mp 168–169° dec, that had precipitated was removed by filtration. Acidification of the filtrate to pH 1.0 gave 0.8 g of solid which was shown to be a mixture of two major products on tlc.

This mixture was chromatographed with silica gel (solvent $CHCl_3$–MeOH–AcOH 90:10:3) to give **3f** (240 mg) and 4-(6-methylthio-7*H*-purin-7-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric acid (**5f**, 140 mg). Recrystallization of **5f** from 50% EtOH gave colorless needles: mp 200–201°; $[\alpha]^{25}D$ +154.5° (c 1.0, 0.1 *N* NaOH); nmr ($CDCl_3$) δ 1.1–2.1 (m, 10 H), 2.80 (s, 3 H), 4.5–5.2 (m, 4 H), 8.41 (s, 1 H), 8.87 (s, 1 H).

Anal. Calcd for $C_{16}H_{20}N_4O_4S$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.79; H, 5.50; N, 15.14.

The total yield of **3f** was 10.04 g (54.6%) and the yield of **5f** was determined to be approximately 5.3% by integration of the nmr spectrum of the crude mixture of **3f** and **5f**. In other run, the whole yield of **3f** and **5f** was 67%.

4-(6-Amino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (3a). A. From 4-(6-Methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (5f).—A solution of **5f** (1.0 g) in concentrated ammonium hydroxide (50 ml) was heated in a sealed tube at 140–145° for 15 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was dissolved in dilute ammonium hydroxide (5 ml). The solution was passed through a column of Amberlite IRC-50 (H form, 20 ml) and the column was washed with H_2O (200 ml). The eluate and washing was concentrated to a volume of 10 ml *in vacuo*. The concentrated solution was acidified to pH 3.5 with 2% formic acid and the solid that had formed was collected by filtration to give **3a** as colorless needles, yield 0.52 g (57%), mp 226–229° dec. This product was identical in its uv and ir spectra with those of **3a** obtained by the reaction of the sodium salt of adenine with the lactone **2**.

B. From 4-(6-Amino-2-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (3e).—A suspension of **3e** (2 g, 5.3 mmol) and freshly prepared Raney nickel (10 g) in EtOH (100 ml) was refluxed with stirring for 3 hr. The Raney nickel was filtered off and washed with 80% EtOH. The filtrate, after decolorization with charcoal, was concentrated to a small volume *in vacuo* and allowed to stand at room temperature overnight. The solid that had formed was collected by filtration, washed with cold EtOH, and dried. The compound (mp 226–228° dec), thus obtained, was identified with an authentic sample of **3a**.

4-(6-Amino-7*H*-purin-7-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (5a). A. From 4-[6-(*N*,*N*-Dimethylaminomethyleneamino)-7*H*-purin-7-yl]-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (5c).—A solution of **5c** (3.0g) in 5% ammonium hydroxide (30 ml) was heated at 80–90° for 45 min. After cooling, the solution was acidified to pH 3.5 with 10% hydrochloric acid and the solid that had precipitated was removed by filtration. The solid was found to be unchanged starting material **5c** (recovery of 1.4 g, 46.7%). The filtrate was allowed to stand at room temperature for 2 hr, and the precipitate that had formed was collected by filtration to give **5a** (1.1 g, mp 235–237° dec). Recrystallization from DMF–H_2O (1:1) gave analytically pure **5a** as colorless prisms, yield 0.4 g (15.5%), mp 242–244° dec.

Anal. Calcd for $C_{15}H_{19}N_5O_4$: C, 54.04; H, 5.75; N, 21.01. Found: C, 53.88; H, 5.81; N, 21.06.

B. From 4-(6-Methylthio-7*H*-purin-7-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (5f).—A solution of **5f** (200 mg) in concentrated ammonium hydroxide (10 ml) was heated in a sealed tube at 140–145° for 15 hr, and the reaction mixture was treated as described above for the 9 isomer. Recrystallization of the crude product (110 mg) from DMF–H_2O (1:1) gave pure **5a** as colorless prisms, mp 239–241° dec. The uv and ir spectra of this compound were identical with those of **5a** derived from **5c**.

N^6-Benzyleritadenine (11) from 4-(6-Benzylamino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (3b).—A mixture of **3b** (10.0 g), 10% hydrochloric acid (40 ml), and dioxane (10 ml) was heated at 80–90° for 1 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was dissolved in water (about 20 ml). The solution was adjusted to pH 3–4 with

10% sodium hydroxide solution and the precipitate that had formed was collected by filtration and dried to give crude **11** (8.0 g, 98.8%). The crude product was recrystallized from H_2O to yield colorless prisms: mp 208–210° dec; $[\alpha]^{25}D$ +32.0° (*c* 1.0, 0.1 *N* NaOH); nmr (DMSO-d_6) δ 4.0 (m, 2 H), 4.22 (m, 2 H), 4.79 (m, 2 H), 7.30 (m, 5 H), 8.04 (s, 1 H), 8.20 (s, 1 H), 8.25 (s, 1 H); uv max ($\epsilon \times 10^{-3}$) 268.5 nm (21.0) at pH 1.3, 271.5 (22.3) at pH 7, 271.5 (22.9) at pH 12.5.

The uv spectrum of the product was identical with that of 9-benzyl-6-benzylaminopurine.[17]

Anal. Calcd for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.40. Found: C, 56.03; H, 4.92; N, 20.45.

N^6-Benzyl-3-isoeritadenine (12) from 4-(6-Benzylamino-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (4b).—A mixture of **4b** (2.0 g), 10% hydrochloric acid (10 ml), and dioxane (10 ml) was heated at 80–90° for 1 hr and treated as in the above experiment. Recrystallization of the product from aqueous EtOH gave **12** (1.0 g, 61.8%) as colorless prisms: mp 237–239° dec; $[\alpha]^{25}D$ +50.7° (*c* 1.0, 0.1 *N* NaOH); uv max ($\epsilon \times 10^{-3}$) 288 nm (23.7) at pH 1.3, 291 (18.8) at pH 7, 292 (17.9) at pH 12.5.

Anal. Calcd for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.40. Found: C, 55.69; H, 4.97; N, 20.43.

The uv spectrum of the product was identical with that of 3-benzyl-6-benzylaminopurine.[17]

3-Isoeritadenine (9). A. From 4-(6-Amino-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (4a).—A solution of **4a** (130 mg) in 10% hydrochloric acid (1 ml) was heated at 80° for 30 min. The reaction mixture was evaporated to dryness *in vacuo* and the residue was dissolved in H_2O (2 ml). This solution was adjusted to pH 3.0 with 10% aqueous NaOH solution and the resulting solids were collected by filtration, yield 70 mg (71%). Recrystallization from H_2O gave 3-isoeritadenine (**9**) as colorless prisms, mp 295–297° dec. The ir and uv spectra of this sample were identical with those of **9** obtained *via* direct hydrolysis of the mixture (**3a** and **4a**).

The ethyl ester of 3-isoeritadenine (**9**) was prepared by esterification of **9** with EtOH in the presence of H_2SO_4, mp 218–220° (EtOH).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.98. Found: C, 47.03; H, 5.42; N, 24.98.

B. From 4-(6-Amino-8-methylthio-3*H*-purin-3-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (4d).—A suspension of **4d** (100 mg) and freshly prepared Raney nickel (1 ml) in 10 ml of 5% aqueous sodium bicarbonate solution was refluxed for 2.5 hr. The Raney nickel was removed by filtration and the clear filtrate was acidified with 10% hydrochloric acid. The acidic solution was heated at 80–90° for 1 hr and concentrated to a volume of 2 ml *in vacuo*. This concentrated solution was adjusted to pH 3, and the solid that had separated was collected by filtration to give crude 3-isoeritadenine (**9**). Purification of the crude product was unsuccessful; so identification was made by the criteria of uv spectra and the behaviors on paper electrophoresis and ion-exchange chromatography.[18]

7-Isoeritadenine (10) from 4-[6-(*N*,*N*-Dimethylaminomethyleneamino)-7*H*-purin-7-yl]-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (5c).—A solution of **5c** (1.0 g) in 10% hydrochloric acid (10 ml) was heated at 80–90° for 1 hr. After cooling, the solution was adjusted to pH 3.5, and the solid that had precipitated was collected by filtration, yield 0.6 g (90.8%), mp 278–279° dec. Recrystallization from DMF–H_2O (1:2, 180 ml) gave pure **10** as colorless prisms: yield 0.35 g; mp 278–279° dec; $[\alpha]^{20}D$ +59.1° (*c* 1.0, 0.1 *N* NaOH); nmr (D_2O–NaOD) δ 4.55–5.0 (m, 4 H), 8.55 (s, 1 H), 8.60 (s, 1 H); uv max ($\epsilon \times 10^{-3}$) 275 nm (14.1) at pH 1.3, 272.5 (10.3) at pH 6.5, 272.5 (10.4) at pH 12.5.

Anal. Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.67. Found: C, 42.70; H, 4.32; N, 27.54.

This compound was identical in its ir and uv spectra with an authentic sample of 7-isoeritadenine (**10**) that was prepared unambiguously *via* methyl 5-(5′-amino-4′-cyanoimidazol-3′-yl)-2,3-*O*-isopropylidene ribofuranoside.[11] The ethyl ester of 7-isoeritadenine (**10**) was prepared by esterification of **10** with EtOH in the presence of H_2SO_4, mp 183–185°, colorless leaflets from EtOH.

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.95; H, 5.51; N, 25.06.

Eritadenine (8). A. From 4-(6-Amino-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (3a).—A solution of **3a** (400 mg) in 10% hydrochloric acid (3 ml) was heated at 80° for 30 min. The reaction mixture was evaporated to dryness *in vacuo* and the residue was dissolved in H_2O (3 ml). This solution was adjusted to pH 3.0 with 10% aqueous NaOH solution and the resulting solids were collected by filtration, yield 270 mg (89%), mp 259–260° dec.

B. From 4-(6-Benzylamino-9*H*-purin-9-yl)-2(*R*),3(*R*)-dihydroxybutyric Acid (3b).—To a solution of **3b** (1.0 g) in liquid ammonia was added with stirring sodium (0.2 g) in pieces during the course of 30 min. The reaction mixture was stirred at room temperature until ammonia distilled away. The residue was dissolved in a few milliliters of H_2O and the solution was neutralized with 10% hydrochloric acid. This neutralized solution was passed through a column of Amberlite IR-120 (H form, 30 ml) and the column was washed with H_2O. The adsorbed substance was eluted with 5% ammonium hydroxide and the eluate was evaporated to dryness *in vacuo*. The residue was dissolved in a small amount of H_2O and the solution was adjusted to pH 3.5. The solid that had formed was collected by filtration. The crude product was dissolved in dilute aqueous sodium hydroxide solution, and the solution was acidified to pH 3.5 with 10% hydrochloric acid. The crystals that had precipitated were collected by filtration and dried to give eritadenine (**8**), yield 100 mg (13.7%).

C. From 4-(6-Amino-2-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-dihydroxybutyric Acid (13).—A suspension of **13** (2 g, 6.7 mmol) and freshly prepared Raney nickel (5 g) in 5% ammonium hydroxide (100 ml) was refluxed with stirring for 3 hr. The Raney nickel was filtered off and washed with H_2O. The filtrate and washing was evaporated to dryness *in vacuo*, and the residue was dissolved in 40 ml of H_2O. The solution was treated with charcoal and filtered. Acidification of the filtrate to pH 3 with 80% formic acid gave **8**, which was collected by filtration and washed H_2O. Recrystallization from H_2O gave eritadenine (**8**), yield 800 mg (47%), mp 262° dec.

D. From 4-(6-Amino-8-methylthio-9*H*-purin-9-yl)-2(*R*),3(*R*)-cyclohexylidenedioxybutyric Acid (3d).—A suspension of **3d** (100 mg) and freshly prepared Raney nickel (1 ml) in 5% aqueous sodium bicarbonate solution was refluxed for 2.5 hr. The Raney nickel was filtered off and the filtrate was acidified with 10% hydrochloric acid. The acidic solution was heated at 80–90° for 1 hr and concentrated to a volume of 2 ml *in vacuo*. This concentrated solution was adjusted to pH 3, and the solid that had separated was collected by filtration to give crude eritadenine (**8**). An attempt to purify the crude product was unsuccessful, so identification was made by the criteria of uv spectra and the behaviors on paper electrophoresis and ion-exchange chromatography.

The eritadenine (**8**) that was obtained in these experiment was identical in its uv and ir spectra with natural eritadenine (**8**).

Registry No.—**1c**, 28856-55-5; **2**, 28875-69-6; **3a**, 28875-70-9; **3b**, 28875-71-0; **3d**, 28875-72-1; **3e**, 28875-73-2; **3f**, 28875-74-3; **4a**, 28875-75-4; **4b**, 28875-76-5; **4d**, 28875-77-6; **5a**, 28875-78-7; **5c**, 28875-79-8; **5f**, 28875-80-1; **7**, 28875-81-2; **8**, 25486-40-2; **8** Na salt, 28875-83-4; **9**, 28875-84-5; **9** Na salt, 28875-85-6; **9** ethyl ester, 28875-86-7; **10**, 28875-87-8; **10** ethyl ester, 28875-88-9; **11**, 28875-89-0; **12**, 28875-90-3; **13**, 28875-91-4.

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The Use of Phenylhydrazine and Substituted Phenylhydrazines for Papain-Catalyzed Resolutions of Racemic *N*-(Benzyloxycarbonyl)alanine

JOHN LEO ABERNETHY,*[1] ELIO ALBANO, AND JOHN COMYNS

Department of Chemistry, California State Polytechnic College, Pomona, California 91728

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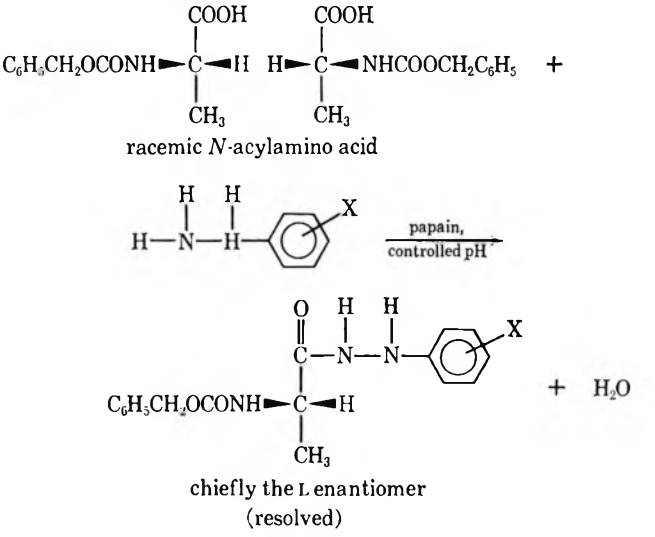
Papain-catalyzed reactions have been carried out between phenylhydrazine, ring-substituted phenylhydrazines, and N^1-methyl-N^1-phenylhydrazine, and four *N*-acylamino acids, namely, hippuric acid, *N*-(benzyloxycarbonyl)-glycine, *N*-(benzyloxycarbonyl)-L-alanine, and N-(benzyloxycarbonyl)-DL-alanine. Thirty-six arylhydrazides were produced. Twelve resolutions of the racemic *N*-acylamino acid were brought about by using different arylhydrazines, due to the chirality of papain. Optical rotations showed that the per cent of L enantiomer varied from about 82 to 99.9%, depending on the arylhydrazine that was used. When the *N*-acylamino acid was *N*-(benzyloxycarbonyl)glycine, the reaction with phenylhydrazine displayed an optimum pH of about 4.0. With N^1-methyl-N^1-phenylhydrazine, the optimum pH was about 4.75.

Interest in resolutions of racemic mixtures and in asymmetric syntheses has been greatly enhanced in recent years because of accelerated attention given to the intricate nature of the origin and perpetuation of life as it exists on earth.[2-4] This report systematically extends studies centered about the behavior of *N*-acylamino acids toward amino-containing bases under papain catalysis. Particular attention was given to the extent of resolution shown by the products from the racemic *N*-acylamino acid that was included for investigation.

The amino bases involved phenylhydrazine, fluorophenylhydrazines, nitrophenylhydrazines, tolylhydrazines, methoxyphenylhydrazines, and N^1-methyl-N^1-phenylhydrazine. All of these were subjected to papain-catalyzed reactions with hippuric acid, *N*-(benzyloxycarbonyl)glycine, *N*-(benzyloxycarbonyl)-L-alanine, and *N*-(benzyloxycarbonyl)-DL-alanine. It was important to determine the optimum pH for the reaction between phenylhydrazine and *N*-(benzyloxycarbonyl)-glycine. A similar determination was made for the reaction between N^1-methyl-N^1-phenylhydrazine and this same *N*-acylamino acid. Other data permit conclusions to be drawn concerning properties of products such as melting points, optical rotations, and relative reaction rates from a qualitative viewpoint.

Resolutions of this racemic *N*-acylamino acid can be represented by the equation shown in column 2. It is well known that the chirality of papain gives preference for the L enantiomer in these reactions through formation of a thio ester[5-7] at the single, existent mercapto group[8] of L-cysteine residue no. 25, when counted from the amino terminal. For this reason, papain has long been classified as a sulfhydryl enzyme.[9] Elucidation of the complete structure of crystalline papain,[10] with its 212 residues, has been achieved through chemical methods[11] and crystallographic analysis.[12]



Results and Discussion

The first experimental work that utilized papain in reversing its proteolytic action was reported by Bergmann and Fraenkel-Conrat[13] in 1937. Both aniline and phenylhydrazine were used with hippuric acid and *N*-(benzyloxycarbonyl)glycine to form the anilides and phenylhydrazides. Although aniline was then used to resolve *N*-(benzyloxycarbonyl)-DL-alanine, nothing else was done to incorporate substituted phenylhydrazines. An optimum pH of 4.0 was found by us for the formation of *N*-(benzyloxycarbonyl)glycine phenylhydrazide, while a pH optimum of 4.75 was exhibited for the production of the corresponding N^1-methyl-N^1-phenylhydrazide. These are shown in Figure 1. All reactions that used ring-substituted phenylhydrazines were buffered at pH 4.0.

The percentage of L enantiomer in the resultant hydrazides can be used as a standard for comparing the degree of resolution of the *N*-acylamino acid. This is given by the familiar equation

$$\begin{matrix}\text{per cent L enantiomer}\\ \text{in } N\text{-acylamino acid}\\ \text{phenylhydrazide}\end{matrix} = \frac{{}^1/_2([\alpha]_{\text{pure L}} + [\alpha]_{\text{mixture}})}{[\alpha]_{\text{pure L}}} \times 100$$

where $[\alpha]_{\text{pure L}}$ and $[\alpha]_{\text{mixture}}$ are the specific rotations, respectively, of products from the *N*-acyl-L-amino acid and the *N*-acyl-DL-amino acid for each amino base used.

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TABLE I

PER CENT OF L ENANTIOMER PRESENT IN ARYLHYDRAZIDES FORMED FROM *N*-(BENZYLOXYCARBONYL)-DL-ALANINE BY THE RESOLVING CAPACITY OF PAPAIN DUE TO ITS CHIRALITY

Arylhydrazine reactant	L enantiomer in product, %	Arylhydrazine reactant	L enantiomer in product, %
Phenylhydrazine	88.2	*o*-Tolylhydrazine	91.2
N^1-Methyl-N^1-phenylhydrazine	82.3	*m*-Tolylhydrazine	93.3
o-Methoxyphenylhydrazine	95.7	*p*-Tolylhydrazine	96.3
p-Methoxyphenylhydrazine	88.2	*o*-Fluorophenylhydrazine	99.9
o-Nitrophenylhydrazine	99.1	*m*-Fluorophenylhydrazine	99.0
m-Nitrophenylhydrazine	99.4	*p*-Fluorophenylhydrazine	98.8

Table I shows that the N^1-methyl-N^1-phenylhydrazide contained the lowest percentage of the L enantiomes, while the *o*-fluorophenylhydrazide contained the highest percentage. Substitution with a methyl group on the N^1 position of phenylhydrazine does substantially reduce the percentage of the L enantiomer in the product. No general correlation with other locations of substituents can be made.

In comparing the specific rotations of the arylhydrazides produced from pure *N*-acyl-L-amino acid, it is evident that the N^1-methyl-N^1-phenylhydrazide (−16.4°) has a much lower absolute value than any of the others (−23.0 to −33.0°), when measured in pyridine as the solvent. For the nitrophenylhydrazides, it was necessary to use 2-methoxyethanol as the solvent due to impaired visibility in pyridine. The *o*-nitro substituent caused a much greater specific rotation (−54.7°) than the *m*-nitro substituent (−34.4°). There is no general correlation between specific rotations and positions of substituents on the ring.

A general relationship does hold for melting points of any set of three arylhydrazides produced from three *N*-acylamino acids and a given arylhydrazine. The hippuric arylhydrazide always has the highest melting point, the *N*-(benzyloxycarbonyl)-L-alanine arylhydrazide is intermediate, and the *N*-(benzyloxycarbonyl)-glycine arylhydrazide is lowest, as shown in Table II.

The observed rates of formation of N^1-methyl-N^1-phenylhydrazides were very slow, particularly when the L- or racemic *N*-acylamino acid was used. The methyl group on the *N*-acylamino acid and on the hydrazino group appears to cause steric hindrance as the arylhydrazine approaches the acylated enzyme. The basicity of the NH_2 group is less sensitive to resonance or inductive properties of the ring substituents in the arylhydrazines[14] than in anilines[15] because of the insulating effect of the intervening NH. Similarly, steric effects are less apparent with arylhydrazines studied here than with anilines previously employed[16] in papain-catalyzed reactions.

Experimental Section

General Procedures.—A Rudolph high-precision polarimeter, purchased through funds from the Research Corp. of N. Y., was used for all polarimetric measurements. Water-jacketed polarimeter tubes, 1 or 2 dm, were used at a controlled temperature of 25°. With the exception of the nitro compounds, the solvent was Eastman Spectro Grade pyridine. Approximately 2% solutions (0.02 g/ml of solution) were made up in 5- or 10-ml volumetric flasks and were incubated in a constant temperature bath at 25°. For the nitro compounds, 2-methoxyethanol was used as the solvent. Nitrogen analyses were determined by the C. F. Geiger Microanalytical Laboratory, Ontario, Calif. All substituted phenylhydrazines were commercially available as their hydrochlorides or free bases. A few of these were also prepared by suitable modifications of established methods.[17-20]

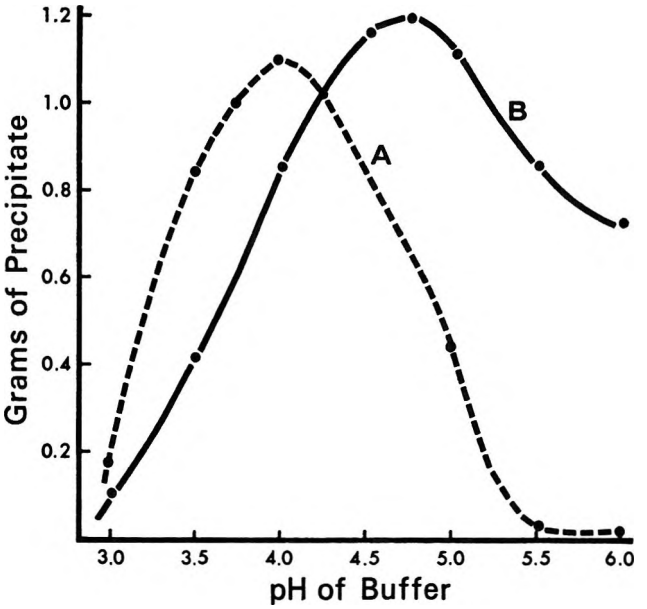

Figure 1.—Dependence of yield on pH for the formation of A, *N*-(benzyloxycarbonyl)glycine phenylhydrazide after 22 hr of incubation at 40°; B, *N*-(benzyloxycarbonyl)glycine N^1-methyl-N^1-phenylhydrazide after 24 hr of incubation at 40°. Solution constituents are as follows: 100 ml of 0.50 *M* buffer; 0.0100 mol of *N*-(benzyloxycarbonyl)glycine; 0.0100 mol of phenylhydrazine (A), or 0.0100 mol of N^1-methyl-N^1-phenylhydrazine (B); 0.250 g of papain; 0.500 g of L-cysteine·HCl·H_2O.

Dependence of Yield on pH.—The dependence of yield on pH was established for two reactions. Phenylhydrazine and N^1-methyl-N^1-phenylhydrazine were each subjected to reactions with *N*-(benzyloxycarbonyl)glycine in appropriate 0.50 *M* buffers at properly spaced pH values. A 100-ml portion of each buffer solution contained 0.0100 mol of each reactant, as well as 0.500 g of L-cysteine·HCl·H_2O and 0.250 g of activated papain. All solutions were filtered before addition of cysteine or papain. The latter two were ground in a mortar and then dissolved in a few milliliters of buffer before addition to the solution. The mortar was rinsed with the solution which was poured back into the reaction flask. Solutions were incubated for 22 hr in the case of phenylhydrazine, or for 24 hr for N^1-methyl-N^1-phenylhydrazine, at 40°. Precipitates were removed by suction filtration, dried in the atmosphere for 2 days, and weighed. Figure 1 shows the dependence of yield on pH for each reaction.

Preparation of Active Papin.—The papaya latex, imported from Ceylon, was donated by the Wallerstein Laboratories of N. Y. The procedure used for extraction and activation of papain was a

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TABLE II

FORMATION OF ARYLHYDRAZIDES BY PAPAIN-CATALYZED REACTIONS BETWEEN ARYLHYDRAZINES AND N-ACYLAMINO ACIDS AT pH 4.0 AND 40°

N-Acylamino acid[a]	Product[b]	Registry no.	Mp, °C	$[\alpha]^{26}D$, deg, in pyridine[c]	% N	
					Found	Calcd
HA	Hippuric phenylhydrazide (P)	6334-93-6	176–178			15.61
BzOC-G	*N*-(Benzyloxycarbonyl)glycine phenylhydrazide	21855-71-0	142–144		13.93	14.04
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine phenylhydrazide	28861-55-4	153–155	−31.9	13.21	13.41
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine phenylhydrazide		152–155	−24.4	Mmp, no depression[d]	
HA	Hippuric *o*-tolylhydrazide (oT)	10517-74-5	167–169		14.88	14.83
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *o*-tolylhydrazide	28861-57-6	66–68		12.67	12.84
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine *o*-tolylhydrazide	28861-58-7	165–166	−33.5	12.67	12.84
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine *o*-tolylhydrazide		165–167	−27.5	Mmp, no depression	
HA	Hippuric *m*-tolylhydrazide (mT)	10517-78-9	179–181		15.05	14.83
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *m*-tolylhydrazide	28861-60-1	124–125		13.70	13.41
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine *m*-tolylhydrazide	28861-61-2	143–144	−27.0	12.66	12.84
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine *m*-tolylhydrazide		143–145	−23.3	Mmp, no depression	
HA	Hippuric *p*-tolylhydrazide (pT)	10517-82-5	175–177		15.12	14.83
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *p*-tolylhydrazide	28861-63-4	133–135		13.75	13.41
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine *p*-tolylhydrazide	28861-64-5	160–162	−29.0	13.10	12.8
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine *p*-tolylhydrazide		162–165	−27.8	Mmp, no depression	
HA	Hippuric *o*-methoxyphenylhydrazide (oM)	28861-65-6	148–149		13.98	14.04
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *o*-methoxyphenylhydrazide	28861-66-7	76–78		12.50	12.76
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine *o*-methoxyphenylhydrazide	28861-67-8	159–160	−24.7	12.50	12.76
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine *o*-methoxyphenylhydrazide		158–160	−22.6	Mmp, no depression	
HA	Hippuric *p*-methoxyphenylhydrazide (pM)	28861-68-9	179–180		14.62	14.69
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *p*-methoxyphenylhydrazide	28861-69-0	140–142		12.69	12.76
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine *p*-methoxyphenylhydrazide	28861-70-3	162–165	−29.4	11.94	12.24
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine *p*-methoxyphenylhydrazide		160–162	−22.4	Mmp, no depression	
HA	Hippuric *o*-fluorophenylhydrazide (oF)	28861-71-4	179–181		14.30	14.63
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *o*-fluorophenylhydrazide	28861-72-5	94–95		13.49	13.25
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine *o*-fluorophenylhydrazide	28861-73-6	151–153	−23.05	13.01	12.77
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine *o*-fluorophenylhydrazide		156–158	−23.00	Mmp, no depression	
HA	Hippuric *m*-fluorophenylhydrazide (mF)	28861-74-7	177–179		14.79	14.63
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *m*-fluorophenylhydrazide	28861-75-8	132–133		13.12	13.25
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine *m*-fluorophenylhydrazide	28861-76-9	156–158	−27.5	12.43	12.77
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine *m*-fluorophenylhydrazide		156–158	−26.9	Mmp, no depression	
HA	Hippuric *p*-fluorphenylhydrazide (pF)	28861-77-0	192–194		14.50	14.63
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *p*-fluorophenylhydrazide	28860-82-4	142–144		12.95	13.25
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine *p*-fluorophenylhydrazide	28860-83-5	173–174	−24.8	12.88	12.77

TABLE I (*Continued*)

N-Acylamino acid[a]	Product[b]	Registry no.	Mp, °C	$[\alpha]^{25}D$, deg, in pyridine[c]	% N Found	% N Calcd
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine *p*-fluorophenylhydrazide		174–176	−24.2	Mmp, no depression	
HA	Hippuric *o*-nitrophenylhydrazide (oN)	28860-84-6	206–208		17.60	17.83
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *o*-nitrophenylhydrazide	28860-85-7	163–165		16.36	16.28
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine[c] *o*-nitrophenylhydrazide	28860-86-8	190–191	−54.7	15.90	15.74
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine[c] *o*-nitrophenylhydrazide		188–190	−53.8	Mmp, no depression	
HA	Hippuric *m*-nitrophenylhydrazide (mM)	28860-87-9	182–184		18.08	17.83
BzOC-G	*N*-(Benzyloxycarbonyl)glycine *m*-nitrophenylhydrazide	28860-88-0	149–150		16.55	16.28
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine[c] *m*-nitrophenylhydrazide	28860-89-1	154–156	−34.4	15.44	15.74
BzOC-DL-A	N-(Benzyloxycarbonyl)alanine[c] *m*-nitrophenylhydrazide		154–156	−34.0	Mmp, no depression	
HA	Hippuric N^1-methyl-N^1-phenylhydrazide (MP)[e]	28860-90-4	161–162		14.47	14.83
BzOC-G	*N*-(Benzyloxycarbonyl)glycine N^1-methyl-N^1-phenylhydrazide	28860-91-5	120–122		13.53	13.41
BzOC-L-A	*N*-(Benzyloxycarbonyl)-L-alanine N^1-methyl-N^1-phenylhydrazide	28860-92-6	152–154	−16.4	12.80	12.84
BzOC-DL-A	*N*-(Benzyloxycarbonyl)alanine N^1-methyl-N^1-phenylhydrazide		150–153	−10.6	Mmp, no depression	

[a] HA = hippuric acid; BzOC-G = *N*-(benzyloxycarbonyl)glycine; BzOC-L-A = *N*-(benzyloxycarbonyl)-L-alanine; BzOC-DL-A = *N*-(benzyloxycarbonyl)-DL-alanine. [b] Abbreviations in parentheses are for the arylhydrazine reactant, used in giving weights of products from reactants in the Experimental Section. [c] Pyridine was used for all solutes except the nitro compounds, in which case 2-methoxyethanol was the solvent. [d] This designates that a mixture of the products from the pure L-amido and the DL-amido acid gave no depression of melting point so that no nitrogen analysis was necessary. Mmp = mixture melting point. [e] The pH for the N^1-methyl-N^1-phenylhydrazides was 4.6 rather than 4.0.

modification of the method used by Bennett and Niemann.[21] Two 100-g samples of the latex were ground in a mortar. Each portion was poured into a 500-ml suction flask that contained 100 ml of distilled water. Each flask was placed in an ice bath and each mixture was stirred for 4 hr with mechanical stirrers. This was followed by two centrifugations of each solution at 2000 rpm for 20 min, each time, to remove undissolved latex. The liquid solutions were decanted into two 500-ml suction flasks in ice baths, in separate dewar flasks. Hydrogen sulfide was passed slowly and simultaneously into each solution for 12 hr. At the end of this period, 5 g of Celite filter aid was added to each flask and each solution was shaken for several minutes. Two centrifugations of each mixture at 2000 rpm, followed by decantation each time, produced a slightly turbid solution which was decanted and suction filtered to remove traces of filter aid. Sufficient methanol was added to each solution to produce a 70% by volume methanolic solution. Precipitates were removed by centrifugation at 2000 rpm for 20 min. The creamed-colored papain paste was scraped into a deep glass dish and dried over P_2O_5 for 5 days. It was necessary to pour off methanol at the end of 24-hr periods and to replenish the P_2O_5. A light tan, brittle solid resulted amounting to about 46 g. It was stored in a refrigerator at 5° in two dark green bottles with screw caps. Its activity was excellent as shown by a trial reaction with phenylhydrazine and *N*-(benzyloxycarbonyl)glycine.

Procedure for Papain-Catalyzed Reactions with Hippuric Acid, *N*-(Benzyloxycarbonyl)glycine, and *N*-(Benzyloxycarbonyl)-L-alanine.—For phenylhydrazine and ring-substituted phenylhydrazines, reactions were run at a pH of 4.0, which was the optimum shown for phenylhydrazine and *N*-(benzyloxycarbonyl)-glycine. A total of 100 ml of 0.50 *M* formic acid buffer was used. Then, 0.0100 mol of the phenylhydrazine or its salt, 0.0100 mol of the *N*-acylamino acid, and 0.250 g of L-cysteine·HCl·H_2O were ground and shaken with 95 ml of the buffer for 25–30 min, followed by suction filtration. The pH was adjusted to 4.0, if necessary. Buffer (5 ml) was used to triturate 0.300 g of papain until it dissolved. It was rinsed with reactant solution into the reaction flask. Incubation was carried out at 40°. Solid was removed by suction filtration at the end of 24 and 28 hr and then dried in the atmosphere for about 2 days and weighed.

Procedure for Papain-Catalyzed Reactions with *N*-(Benzyloxycarbonyl)-DL-alanine.—For these reactions, 0.00600 mol of the phenylhydrazine or its salt was used with 0.0120 mol of *N*-(benzyloxycarbonyl)-DL-alanine. Otherwise the procedure was the same with 100 ml of formic acid buffer, pH 4.0.

Procedure for Papain-Catalyzed Reactions with N^1-Methyl-N^1-phenylhydrazine.—Since the pH optimum was 4.75 for the reaction with *N*-(benzyloxycarbonyl)glycine, a 0.50 *M* acetic acid buffer at pH 4.6 was found to be convenient for these reactions. For hippuric acid, 0.0100 mol of substituted phenylhydrazine and amido acid were employed. For *N*-(benzyloxycarbonyl)-L-alanine and *N*-(benzoyloxycarbonyl)-DL-alanine, so little reaction product was given by the usual method that the amount of solution was increased to 250 ml, while 1.000 g of papain was used and about 0.600 g of L-cysteine·HCl·H_2O. About 0.0250 mol of the *N*-acyl-L-amino amido acid was used, and about the same quantity of the *N*-acyl-DL-amino acid was also used. Several variations were tried and products were accumulated in each case. Only about 0.25 g of product was obtained at the end of 48 hr of incubation at pH 4.6 and 40°.

Hippuric *m*-Tolylhydrazide and Hippuric *p*-Fluorophenylhydrazide.—It was necessary to run several trial experiments to obtain sufficient amounts of these products for purification, for nitrogen analyses, and determination of melting points. In general, about 200 ml of solutions were made up with nearly 0.02 mol of the substituted phenylhydrazide. The same amount of hippuric acid was used with 0.500 g of L-cysteine·HCl·H_2O and 1 g of papain. After 48 hr, between 0.15 and 0.20 g of product was obtained when the usual drying procedure was used. In all trial runs with *p*-nitrophenylhydrazine and any of the *N*-acylamino acids, no product was obtained. This was due to the extreme insolubility of *p*-nitrophenylhydrazine in the buffer at pH 4.0.

Purification Procedures.—When the reaction mixtures were filtered before incubation, clear-cut precipitates were usually obtained by filtration of the product mixtures. After suction filtration and drying the solids in the atmosphere for 48 hr, the solids were stirred with several portions of hot water and removed

(21) E. L. Bennett and C. Niemann, *J. Amer. Chem. Soc.*, **72**, 1798 (1950).

by filtration. This dissolved soluble impurities. They were again dried in the atmosphere and then dissolved in cold methanol and treated with carbon black in the cold for about 10 min. Filtration was repeated four times under suction. Each time meticulously cleaned funnels and flasks were used to ensure complete removal of carbon and insoluble impurities, as well as those adsorbed by the carbon. The clear solutions were poured into petri dishes and allowed to evaporate under the hood. Solids were removed and dried over phosphorus pentoxide in a vacuum desiccator. All nitrophenylhydrazides were deep yellow in color. Other solids took on slight coloration if exposed to the atmosphere too long. This seems to be due to the susceptibility of these substituted hydrazines to slight atmospheric oxidation. Further purification was unnecessary for obtaining correct nitrogen analyses, nor did further purification improve the melting points or optical rotations.

Melting Points.—All melting points were determined by means of a Fisher-Johns melting point apparatus. Corrections were made by the use of several compounds of proper purity and known melting points. A curve was plotted for their measured melting points along with a straight line curve for true melting points, in the usual manner. Substances used were *p*-dichlorobenzene, *m*-dinitrobenzene, benzoic acid, salicylic acid, hippuric acid, and anthracene.

Yields of Arylhydrazides from Listed Reactants.—The reactants and yields for periods of incubation of 0–24 hr (24–48 hr in parentheses) follow (abbreviations for reactants are indicated in Table II; details of the experiments are provided elsewhere in the Experimental Section): HA + P, 0.853 g (0.246 g); BzOC-G + P, 1.370 g (0.223 g); BzOC-L-A + P, 1.576 g (0.0414 g); BzOC-DL-A + P, 1.525 g (0.0203 g); HA + oT, 0.396 g (0.324 g); BzOC-G + oT, 0.821 g (0.314 g); BzOC-L-A + oT, 1.557 g (0.0782 g); BzOC-DL-A + oT, 1.032 g (0.0999 g); HA + mT (see Experimental Section); BzOC-G + mT, 0.619 g (0.105 g); BzOC-L-A + mT, 1.718 g (0.0356 g); BzOC-DL-A + mT, 1.533 g (0.0815 g); HA + pT, 0.654 g (0.223 g); BzOC-G + pT, 1.256 g (0.247 g); BzOC-L-A + pT, 1.360 g (0.0042 g); BzOC-DL-A + pT, 0.378 g (0.0261 g); HA + oM, 0.674 g (0.254 g); BzOC-G + oM, 0.888 g (0.201 g); BzOC-L-A + oM, 2.067 g (0.0419 g); BzOC-DL-A + oM, 0.864 g (0.0086 g); HA + pM, 0.0523 g (0.0202 g); BzOC-G + pM, 0.209 g (0.0185 g); BzOC-L-A + pM, 0.271 g (0.0312 g); BzOC-DL-A + pM, 0.188 g (0.0467 g); HA + oF, 0.925 g (0.207 g); BzOC-G + oF, 1.495 g (0.160 g); BzOC-L-A + oT, 1.154 g (0.0743 g); BzOC-DL-A + oF, 1.353 g (0.0635 g); HA + mF, 0.363 g (0.143 g); BzOC-G + mF, 0.647 g (0.0769 g); BzOC-L-A + mF, 0.173 g (0.0452 g); BzOC-DL-A + mF, 0.361 g (0.0700 g); HA + pF (see Experimental Section); BzOC-G + pF, 0.163 g (0.0475 g); BzOC-L-A + pF, 0.256 g (0.163 g); HA + oN, 0.132 g (0.000 g); BzOC-G + oN, 0.197 g (0.000 g); BzOC-L-A + oN, 0.205 g (0.000 g); BzOC-DL-A + oN, 0.232 g (0.000 g); HA + mN, 0.293 g (0.0717 g); BzOC-G + mN, 0.518 g (0.0850 g); BzOC-L-A + mN, 0.608 g (0.0558 g); BzOC-DL-A + mN, 0.402 g (0.0658 g); HA + MP, 0.000 g (0.203 g); BzOC-G + MP, 0.206 g (0.198 g); BzOC-L-A MP and BzOC-DL-A + MP (see Experimental Section).

Registry No.—Phenylhydrazine, 100-63-0; *N*-(benzyloxycarbonyl)-DL-alanine, 4132-86-9.

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Studies on Reactions of Isoprenoids. XIII.[1] The 1,4-Cycloaddition Reactions of Alloocimene with Various Dienophiles

TADASHI SASAKI,* SHOJI EGUCHI, AND HIROTO YAMADA

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464, Japan

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1,4-Cycloaddition reactions of alloocimene, an isomeric mixture of **1a** and **1b**, with several acetylenic, olefinic, and heterodienophiles were investigated. With cyanoacetylene, alloocimene afforded a 1:1 adduct **2a** and *a 1:2 adduct* **3**; **3** is regarded as a 1,4 cycloadduct of a 1:1 ene product from **1b** to cyanoacetylene. With dimethyl acetylenedicarboxylate, tetracyanoethylene, *p*-benzoquinone, and 4-phenyl-1,2,4-triazoline-3,5-dione, both **1a** and **1b** gave the corresponding 1,4 adducts, but, with nitrosobenzene, only **1a** reacted to afford two isomeric adducts, **11a** and **12a**, having a different orientation. All the 1,4-cycloaddition reactions proceeded primarily by reaction of **1a** rather than **1b**.

Although 1,4-cycloaddition reactions of alloocimene, 2,6-dimethyl-2,4,6-octatriene, with maleic anhydride[2] and dialkyl azodicarboxylate[3] have been studied extensively, those with other dienophiles have apparently not yet been investigated. As an extension of our study on the 1,4-cycloaddition reactions of myrcene,[1,4] this paper deals with the reactions of alloocimene with several acetylenic, olefinic, and heterodienophiles of unsymmetrical structure such as cyanoacetylene and nitrosobenzene. Regiospecific properties of the cycloadditions are discussed.

Results and Discussion

Reaction Conditions.—The alloocimene used in all the reactions was an isomeric mixture of **1a** and **1b**[5] in a 57:43 ratio, since the interconversion of **1a** and **1b** by dienophiles has been reported[2b] and since the separation of **1a** and **1b** requires considerable effort. Reaction conditions, product distribution, and yields as well as the isomer ratios of the recovered alloocimene and the products are summarized in Table I. Reaction temperatures were chosen so as to give the adducts under as mild conditions as possible. The polymerization of alloocimene was not serious under the employed conditions and no polymerization inhibitor was used.

In reactions with acetylenic dienophiles, such as

(1) Part XII of this series: T. Sasaki, S. Eguchi, T. Ishii, and H. Yamada, *J. Org. Chem.*, **35**, 4273 (1970).

(2) (a) J. E. Milks and J. E. Lancaster, *ibid.*, **30**, 888 (1965); (b) E. K. von Gustorf and J. Leitich, *Tetrahedron Lett.*, 4689 (1968), and references cited therein.

(3) E. K. von Gustorf, *ibid.*, 4693 (1968).

(4) T. Sasaki, S. Eguchi, and T. Ishii, *J. Org. Chem.*, **34**, 3749 (1969).

(5) For nomenclature of the two geometrical isomers, **1a** and **1b**, see K. J. Crowley, *ibid.*, **33**, 3679 (1968).

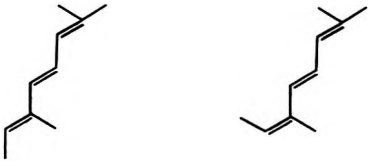
Table I

1,4-Cycloaddition Reactions of Alloocimene (1a and 1b) with Various Dienophiles

Dienophile[a] (solvent)	Reaction Temp, °C	Reaction Time, days	Products (yield, %)[b]	Ratio of a series to b series[c]	Ratio of recovered 1a to 1b[d]
Cyanoacetylene (benzene)	55–60	4	**2a** (56) + **3** (15)	100:0[e]	0:100
Dimethyl acetylenedicarboxylate (benzene)	55–60	4	**5a** + **5b** (66)	89:11	0:100
Tetracyanoethylene (benzene)	20–25	1	**8a** + **8b** (87)	60:40 (61:39)[f]	No recovery
p-Benzoquinone (benzene)	Reflux	0.3	**9a** + **9b** (14)	67:33[g] (72:28)[f]	No recovery
Nitrosobenzene[h] (benzene)	20–25	3	**11a** (32) + **12a** (16)	100:0[i]	23:77
4-Phenyl-1,2,4-triazoline-3,5-dione (*p*-dioxane)	20–25	1	**13a** + **13b** (79)	75:25 (76:24)[f]	No recovery

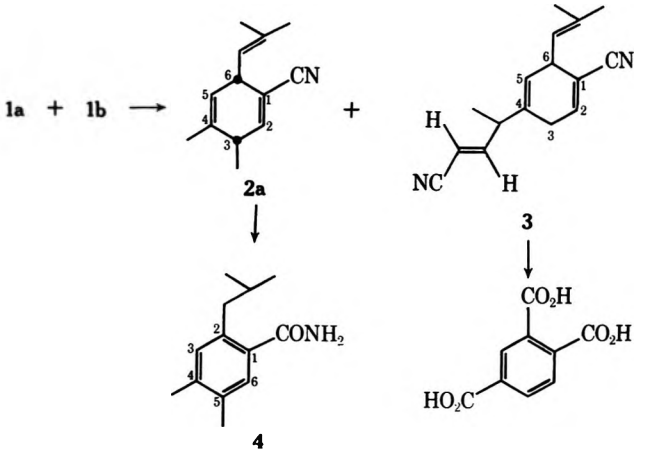
[a] Equimolar amounts of dienophile and alloocimene were used. [b] Products isolated as a mixture of a and b series. All of the a series were isolable from the mixture. [c] Glpc analysis at 150°. [d] Glpc analysis at 100°. [e] For the 1:1 adduct. [f] Nmr analysis. [g] Glpc at 200° was accompanied by some decomposition. [h] The molar ratio of nitrosobenzene to alloocimene was 1:2. [i] For both **11a** and **12a**.

cyanoacetylene and dimethyl acetylenedicarboxylate, alloocimene gave 71 and 66% yields of the adducts, respectively. With chlorocyanoacetylene, however, it afforded only black polymers even under mild conditions (20–25° for 5 days and 0–5° for 2 weeks). With stronger dienophiles, such as tetracyanoethylene and 4-phenyl-1,2,4-triazoline-3,5-dione, alloocimene gave the corresponding adducts in excellent yields even at 20–25°. By contrast, *p*-benzoquinone afforded only a low yield of adduct which was accompanied by unavoidable side products, for example, considerable amounts of quinhydrone. Only **1a** reacted with nitrosobenzene at 20–25° to afford a mixture of adducts which differed in orientation.



1a **1b**

Structure Elucidation of Adducts.—Reaction of alloocimene with cyanoacetylene afforded two products which were separated by distillation. The more abundant of them was a 1:1 adduct on the basis of analysis and mass spectrum and was assigned structure **2a**. In the nmr spectrum, a doublet of doublets ($J_{2,3}$ = 4.5, $J_{2,6}$ = 1.5 Hz) at τ 3.40 assignable to CH=C(CN) supported the postulated mode of the 1,4 cycloaddition, since the reverse orientation would have led to a coupling between C_1 H and C_5 H in addition to those between C_1 H and C_6 H, and C_1 H and C_3 H. Treatment of **2a** with potassium *tert*-butoxide–dimethyl sulfoxide followed by catalytic hydrogenation afforded 2-isobutyl-4,5-dimethylbenzamide (**4**). The nmr spectrum of **4** at 100 MHz exhibited singlets of two aromatic protons at τ 2.82 and 3.06, indicating a *para* relationship between them.[6] Since **2a** revealed only single peak on glpc and since **1a** is more reactive than **1b** in 1,4 cycloadditions due to steric inhibition in the s-cis form of **1b**,[2b] the C_3 and C_6 substituents of **2a** were assumed to be cis to each other. However, since the homoallylic coupling constants could not be determined readily, the



conformation of the 1,4-cyclohexadiene system of **2a** is not known at present.[7]

The second compound was a 1:2 adduct of the formula $C_{16}H_{18}N_2$. In the nmr spectrum (100 MHz), signals characteristic of a 1,4-cyclohexadiene substituted with cyano, isobutenyl, and 1-methyl-3-cyano-2-propenyl groups at C_1, C_6, and C_1, respectively, appeared at τ 3.44, 4.65, 6.24, and 7.30. Ir absorptions at 1660 and 970 cm^{-1} and the value of $J_{2,3}$ = 16 Hz permitted assignment of the trans configuration to the 1-methyl-3-cyano-2-propenyl group. The relative position of the substituents was determined by conversion of this isomer to trimellitic acid. Hence its structure was **3**.

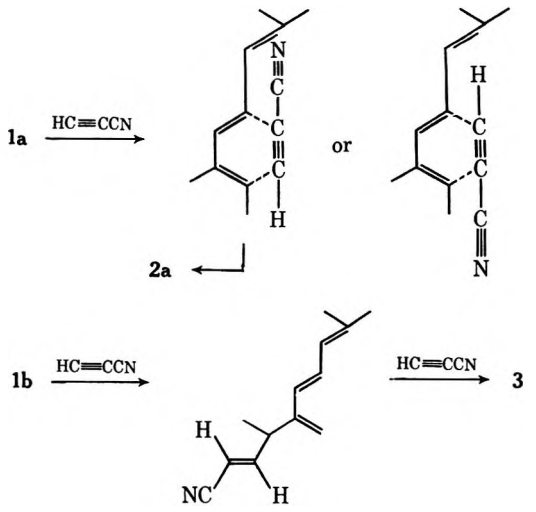
The formation of **3** indicates that **1b** reacted initially as an ene component[8] with a molecule of cyanoacetylene as an enophile to give 1-cyano-3,8-dimethyl-4-methylenenona-1,5,7-triene which reacted further as a diene with a second molecule of cyanoacetylene as a dienophile.

The product of alloocimene and dimethyl acetylenedicarboxylate was a 1:1 adduct whose nmr spectrum was compatible with that of a 1,4 cycloadduct, although the C_6 H signal at τ 6.13 overlapped those of the carbomethoxy protons at τ 6.19 and 6.23, and the C_3 H signal at τ 7.05 appeared as a very broad multiplet which made it difficult to assign stereochemistry. Examination of the recovered alloocimene and the ad-

(6) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 306.

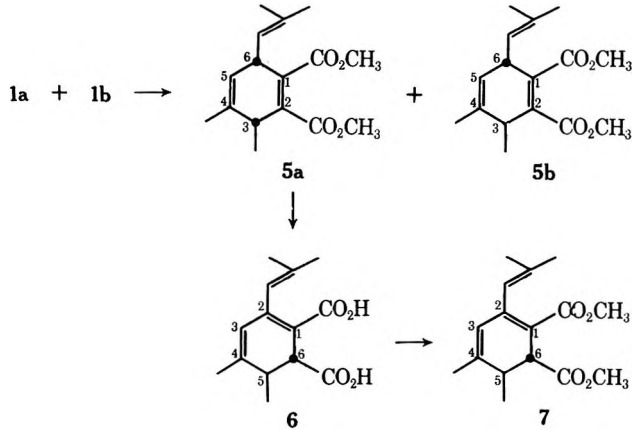
(7) Some conflicting results have recently been reported for simply substituted 1,4-cyclohexadienes. For example, see J. L. Marshall, K. C. Erickson, and T. K. Folsom, *J. Org. Chem.*, **35**, 2038 (1970).

(8) For a review on the ene reaction, see H. M. R. Hoffman, *Angew. Chem. Int. Ed. Engl.*, **8**, 556 (1969).

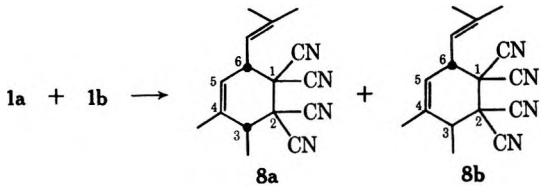


duct revealed that **1b** had remained unreacted, and that the product was a 89:11 mixture of the cis–trans isomers **5a** and **5b**. Pure **5a**, the nmr spectrum of which was practically the same as that of the mixture, was isolated by fractional distillation.

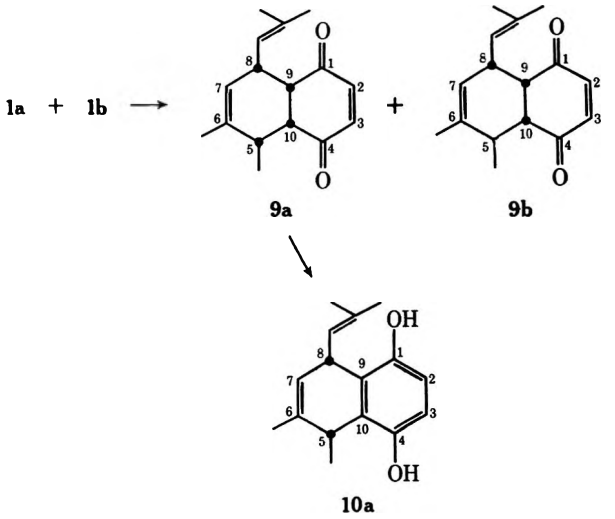
Hydrolysis of **5a** gave a crystalline dicarboxylic acid characterized as **6** by analytical and spectral data; its uv absorption [λ_{max}^{EtOH} 220 and 303 nm (ϵ 8280 and 6480)] was similar to that of 1,6-dicarboxy-4-methyl-1,3-cyclohexadiene (λ_{max}^{EtOH} 296 nm).[9] Brief treatment of **6** with excess diazomethane gave the corresponding dimethyl ester **7** which had nmr signals at τ 7.30 (double q, J = 7.5 and 1.5 Hz) and 6.25 (d, J = 1.5 Hz) due to C_5 H and C_6 H, respectively. The magnitude of $J_{5,6}$ = 1.5 Hz permitted the deduction that the C_5-methyl group was trans to the C_6-carboxyl group.[10] Double bond isomerization of 1,2-dicarboxy-1,4-cyclohexadiene to 1,6-dicarboxy-1,3-cyclohexadiene under hydrolysis conditions has been reported.[11] Hence structure **5a** could be assigned to the original 1:1 adduct.



The reaction of alloocimene with tetracyanoethylene proceeded very smoothly even under mild conditions; no alloocimene was recovered. Since glpc analysis revealed the presence of two peaks in a 61:39 ratio and the nmr spectrum had a pair of doublets at τ 8.37 and 8.46 (C_3 methyl) in a ratio of 6:4, the adduct was a mixture of **8a** and **8b**. The main isomer was isolated in solid form and assigned structure **8a** on the basis of analytical and spectral data (see Experimental Section).



The product from alloocimene and *p*-benzoquinone, $C_{16}H_{20}O_2$, had ir absorptions at 1680, 1650 sh, and 1600 cm^{-1} which suggested the presence of an enedione moiety. The uv spectrum [λ_{max}^{EtOH} 203 and 286 nm (ϵ 20,800 and 897)] was indicative of the presence of a homocisoid type enedione chromophore.[12] The nmr spectrum of the adduct was very similar to that reported for the maleic anhydride adduct of alloocimene,[2] but the appearance of the C_5-methyl protons signals as a pair of doublets at τ 8.80 and 8.88 (J = 7.5 Hz) suggested that the adduct was a mixture of **9a** and **9b** in *ca.* 7:3 ratio. Glpc analysis supported this conclusion. The major isomer was isolated in crystalline form and characterized as **9a** on spectral evidence and by its conversion to **10a**. Chromatography of **9a** on an alumina column resulted in the aromatization of the 1,4-cyclohexadiene ring and formation of **10a** which exhibited strong hydroxyl stretching frequency at 3600–3000 cm^{-1} and uv absorption at 285 nm (ϵ 3460) similar to that of hydroquinone.[13] The nmr spectrum exhibited only one doublet due to the C_5-methyl protons at τ 8.67, thus supporting the purity of **10a**.



In the reaction with nitrosobenzene, the ratio of recovered **1a** to **1b** was 23:77, *i.e.*, considerably enriched in **1b** compared with the original 57:43 composition, thus indicating that **1a** reacted selectively with the dienophile. Distillation and chromatography resulted in isolation of **11a** and **12a** as oils. Both products were 1:1 adducts. The nmr spectrum of one isomer contained a broad singlet at τ 4.71 and a broad quartet at τ 6.24 attributable to H_6 and H_3, respectively, since in

(9) (a) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *J. Amer. Chem. Soc.*, **72**, 3542 (1950); (b) V. F. Kucherov and N. Ya. Grigor'eva, *Dokl. Akad. Nauk SSSR*, **128**, 547 (1959); *Chem. Abstr.*, **54**, 7583*d* (1960).

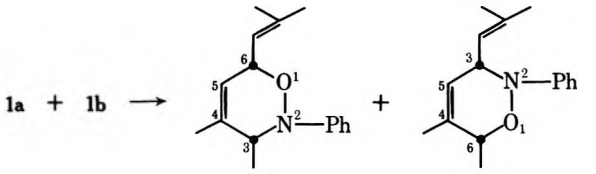
(10) For example, see ref 6, p 281.

(11) N. Ya. Grigor'eva and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2196 (1962); *Chem. Abstr.*, **58**, 11234*h* (1963).

(12) The maximum of 5,6-dimethyl-5,6-dialkylcyclohex-2-ene-1,4-dione appears at 224 nm. The apparent maximum at 203 nm in the spectrum of the adduct is possibly attributable to overlap with an isolated double bond absorption; see A. I. Scott, *Int. Ser. Monogr. Org. Chem.*, **7**, 61 (1964).

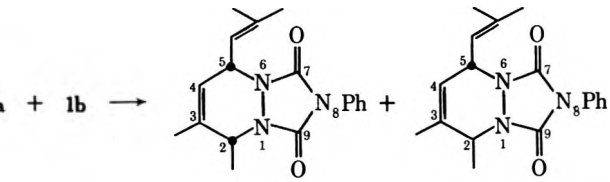
(13) λ_{max}^{EtOH} 295 nm (ϵ 3100): G. L. Schmur, L. A. Cohen, and B. Witkop, *J. Amer. Chem. Soc.*, **81**, 2228 (1959).

the 3,6-dihydro-1,2-oxazine ring system H_6 appears generally at the lower field than H_3.[14] Hence this isomer was **11a**. The other isomer exhibited a broad quartet at τ 6.25 and a broad singlet at τ 5.12, which were assignable to C_6H and C_3H respectively. In view of the fact that cycloaddition of *p*-chloronitrosobenzene to 1,4-disubstituted 1,3-diene produces predominantly their adduct having a more bulky group at the C_6 position,[15] this isomer was assigned formula **12a**.



11a **12a**

No alloocimene was recovered from the reaction of alloocimene with 4-phenyl-1,2,4-triazoline-3,5-dione (Table I). From the product, a mixture of **13a** and **13b** by nmr and glpc analysis, one isomer was isolated after repeated recrystallization and assigned formula **13a** because its nmr spectrum exhibited no signal at τ 8.68 expected from the C_2-methyl protons of **13b**.



13a **13b**

These results indicate clearly that **1a** is a more reactive diene than **1b** where considerable steric hindrance in the s-cis form indispensable to 1,4-cycloaddition reaction exists. It should also be noted that **1b** reacted as an ene rather than as a diene with cyanoacetylene to afford an ene adduct which then reacted with a second molecule of cyanoacetylene to give finally the 1:2 adduct **3**.

The formation of **2a** in the 1,4 cycloaddition of **1a** and cyanoacetylene is an interesting example of a reaction where a symmetry-allowed second-order interaction[16] governs the direction of cycloaddition, because the secondary orbital interaction between the 2,3 double bond of **1a** and the cyano group is possible at the transition state to **2a**.

Experimental Section[17]

General Procedure for 1,4-Cycloaddition Reactions of Alloocimene.—An equimolar mixture of freshly distilled alloocimene, bp 83–85° (22 mm), $n^{18}D$ 1.5382, and a dienophile was allowed to react under conditions given in Table I. Dienophiles such as cyanoacetylene,[18] chlorocyanoacetylene,[19] nitrosobenzene,[20] and 4-phenyl-1,2,4-triazoline-3,5-dione[21] were prepared by known methods and others were commercially available.

1-Cyano-3,4-dimethyl-6-isobutenyl-1,4-cyclohexadiene (2a) and 1-Cyano-4-(1-methyl-3-cyano-2-propenyl)-6-isobutenyl-1,4-cyclohexadiene (3).—A mixture of 13.6 g (0.100 mol) of alloocimene and 5.50 g (0.108 mol) of cyanoacetylene in 100 ml of benzene was heated in a sealed tube at 55–60° for 4 days. Products were purified by distillation under reduced pressure to give 10.5 g (56%) of **2a** and 3.47 g (15%) of **3** both as colorless oils. **2a**: bp 92–93° (0.35 mm); $n^{22}D$ 1.5032; ir (neat) 2924, 2230, 1660, 1630, 1450, 1380, and 835 cm^{-1}; nmr ($CDCl_3$) τ 3.40 (d, d, $J_{2,3}$ = 4.5 Hz, $J_{2,6}$ = 1.5 Hz, 1, C_2H), 4.65 (m, 1, C_5H), 5.10 (br d, J = 12.0 Hz, 1, C=CH), 6.20 (br m, 1, C_6H), 7.33 (br m, 1, C_3H), 8.18 (s, 9, C_4CH_3 and $C(CH_3)_2$), and 8.81 (d, J = 7.5 Hz, 3, C_3CH_3); mass spectrum *m/e* (rel intensity) 187 (0.7), 186 (5.7), 185 (29.5), 171 (84.2), 158 (20.0), 157 (32.0), 146 (21.6) 145 (87.0), 144 (51.0), 131 (100.0), 119 (31.8), 116 (30.7), 91 (19.3), 77 (26.1), and 55 (28.4).

Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.54; H, 9.29; N, 7.17.

3: bp 175–178° (0.08 mm); $n^{22}D$ 1.5409; ir (neat) 2924, 2230, 1660, 1628, 970, 860, and 827 cm^{-1}; nmr ($CDCl_3$, 100 MHz) τ 3.38 (d, d, J = 6.5 and 16.0 Hz, 1, C(CN)=CH), 3.44 (m, 1, C_2H), 4.65 (m, 1, C_5H), 4.68 (d, d, J = 16.0 and 1.5 Hz, 1, CH(CN)=C), 5.17 (d, J = 10.0 Hz, 1, C=CH), 6.24 (m, 1, C_6H), 7.05 (quintet, J = 6.5 Hz, 1, CH), 7.30 (m, 2, C_3H), 8.24 (s, 6, $C(CH_3)_2$), and 8.82 (d, J = 6.5 Hz, 3, CH_3); mass spectrum *m/e* (rel intensity) 238 (8.5), 237 (40.0), 236 (28.0), 235 (39.0), 223 (41.0), 195 (58.5), 158 (62.2), 116 (100.0), 91 (23.7), and 53 (65.9).

Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.90; H, 7.60; N, 11.33.

2-Isobutyl-4,5-dimethylbenzamide (4) from 2a.—A mixture of 1.87 g (10.0 mmol) of **2a** and 1.70 g (15.0 mmol) of potassium *tert*-butoxide in 10 ml of dry dimethyl sulfoxide was stirred for 2 weeks at room temperature under nitrogen. The mixture was diluted with water, neutralized with 10% hydrochloric acid, and extracted with ether (five 30-ml portions). The ether extract was washed with 10% aqueous sodium hydroxide and water successively and dried (Na_2SO_4). Removal of ether gave solid residue which was purified on a silica gel column to afford an amide derivative (105 mg). Catalytic hydrogenation of the amide with 10% palladium on charcoal in ethanol gave **4** (95 mg) as crystals from *n*-hexane–dichloromethane: mp 127–128°; ir (KBr) 3375, 3190, 2920, 1645, 1452, 1380, 1230, and 880 cm^{-1}; nmr ($CDCl_3$, 100 MHz) τ 2.82 (s, 1, C_6H), 3.06 (s, 1, C_3H), 3.76–4.74 (br m, 2, $CONH_2$), 7.36 (d, J = 7.5 Hz, 2, Ar CH_2), 7.79 (s, 6, C_4CH_3 and C_5CH_3), 8.14 (m, 1, $CH_2CH(CH_3)_2$), and 9.14 (d, J = 7.0 Hz, 6, $CH(CH_3)_2$).

Anal. Calcd for $C_{13}H_{19}NO \cdot {}^1/_2H_2O$: C, 72.86; H, 9.41; N, 6.54. Found: C, 72.78; H, 9.55; N, 6.48.

Trimellitic Acid from 3.—A mixture of 0.950 g (3.99 mmol) of **3** and 0.430 g (13.4 mg-atom) of sulfur was heated for 0.5 hr at 205–215°. The resulted dark brown oil was refluxed with 50 ml of 10% aqueous sodium hydroxide for 4 hr. Heating was continued for another 20 hr; during this time 4.00 g (25.3 mmol) of potassium permanganate was added. After decomposition of the excess permanganate with ethanol, the mixture was filtered while still hot. The filtrate was neutralized with concentrated hydrochloric acid and extracted with ether (five 200-ml portions). Work-up gave 0.450 g (53%) of trimellitic acid identified with the superimposable ir spectrum on that of an authentic sample.

1,2-Dimethoxycarbonyl-3,4-dimethyl-6-isobutenyl-1,4-cyclohexadiene (5a).—The reaction of 13.6 g (0.100 mol) of alloocimene with 14.2 g (0.100 mol) of dimethyl acetylenedicarboxylate in 100 ml of benzene gave 18.3 g (66%) of a 89:11 mixture of **5a** and **5b** as an oil, bp 140–142° (0.4 mm), $n^{22}D$ 1.5040. Redistillation afforded pure **5a**: bp 141–142°; $n^{22}D$ 1.5041; ir (neat) 2975, 1720, 1642, 1450, 1380, 1265, and 835 cm^{-1}; uv max (EtOH) 206 and 234 nm inflection (ϵ 18,800 and 7370); nmr ($CDCl_3$) τ 4.65 (m, 1, C_5H), 5.20 (br d, J = 11.0 Hz, 1, C=CH),

(14) (a) G. Kresze and J. Firl, *Tetrahedron*, **24**, 1043 (1968); (b) see also ref 1.

(15) G. Kresze and J. Firl, *Tetrahedron Lett.*, 1163 (1965).

(16) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965).

(17) Microanalyses were performed with a Perkin Elmer 240 elemental analyzer. Melting points were determined with a Yanagimoto hot-stage type melting point apparatus an are uncorrected; boiling points are also uncorrected. Ir spectra were obtained with a JASCO IR-S spectrometer and uv spectra with a JASCO ORD/UV5 spectrometer. Nmr spectra were taken with Varian A-60 and/or HA-100 spectrometers using TMS as internal standard, and mass spectra with a JEOL JMS-01SG spectrometer at 70 eV. Glpc analyses were performed with a K-23 Hitachi gas chromatograph using a 2-m column packed with silicone SE-30 and/or Apiezon L.

(18) See footnote 18 in ref 4.

(19) See footnote 19 in ref 4.

(20) G. H. Coleman, C. M. McCloskey, and F. A. Stuart, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 668.

(21) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc. C*, 1905 (1967).

6.13 (br m, 1, C_6 H), 6.19 and 6.23 (s, each 3, $2COOCH_3$), 7.05 (br m, 1, C_3 H), 8.27 (s, 9, C_4 CH_3 and $C(CH_3)_2$), and 8.70 (d, J = 7.5 Hz, 3, C_3 CH_3); mass spectrum m/e (rel intensity) 278 (39.3), 263 (36.9), 231 (100.0), 219 (30.3), 199 (25.4), 187 (44.3), 159 (48.4), 149 (36.9), 105 (35.2), and 91 (38.5).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.77; H, 7.81.

1,6-Dicarboxy-2-isobutenyl-4,5-dimethyl-1,3-cyclohexadiene (6) and Its Dimethyl Ester (7) from 5a.—A suspension of 1.00 g (3.60 mmol) of **5a** in 50 ml of 20% aqueous sodium hydroxide was refluxed for 1 day. The cooled mixture was washed twice with ether and neutralized with 5% sulfuric acid to afford a turbid solution which was extracted with ether (five 100-ml portions). The ether extract was dried (Na_2SO_4) and evaporated to give an oily residue which on crystallization from chloroform–ether afforded 0.370 g (36%) of **6** as colorless prisms: mp 178–181° dec; ir (KBr) 3000–2800, 1665, 1440, 1415, 1380, and 840 cm^{-1}; nmr ($(CD_3)_2SO$) τ −2.00–0.00 (br m, 2, disappeared on deuteration, 2COOH), 3.61 (m, 1, C_3 H), 4.33 (d, J = 1.7 Hz, 1, C=CH), 6.58 (br s, 1, C_6 H), 7.37 (br q, J = 7.5 Hz, 1, C_5 H), 8.19 (m, 6, $C(CH_3)_2$), 8.38 (s, 3, C_4 CH_3), and 9.03 (d, J = 7.5 Hz, 3, C_5 CH_3); mass spectrum m/e (rel intensity) 250 (38.1), 191 (30.2), 189 (14.3), 187 (23.8), 173 (25.4), 119 (25.4), and 73 (100.0).

Anal. Calcd for $C_{14}H_{18}O \cdot 2H_2O$: C, 58.73; H, 7.75. Found: C, 59.01; H, 8.05.

Treatment of **6** with excess diazomethane in ether at 0–10° for several minutes afforded quantitatively the dimethyl ester **7** as an oil: $n^{21}D$ 1.5241; ir (neat) 2960, 1715, 1700, 1685 sh, 1635 sh, 1565, 1434, 1378, 1280, 1225, and 873 cm^{-1}; uv max (EtOH) 204 and 295 nm (ϵ 11,300 and 5900); nmr ($CDCl_3$) τ 3.67 (br s, 1, C_3 H), 4.36 (m, 1, C=CH), 6.25 (d, J = 1.5 Hz, 1, C_6 H), 6.31 and 6.41 (s, each 3, $2COOCH_3$), 7.30 (d, q, J = 1.5 and 7.5 Hz, 1, C_5 H), 8.16 (d, J = 1.5 Hz, 6, $C(CH_3)_2$), 8.35 (s, 3, C_4 CH_3), and 8.98 (d, J = 7.5 Hz, C_5 CH_3).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.12; H, 7.89.

1,1,2,2-Tetracyano-3,4-dimethyl-6-isobutenyl-4-cyclohexene (8a).—The reaction product from 1.36 g (10.0 mmol) of alloocimene and 1.28 g (10.0 mmol) of tetracyanoethylene was purified by chromatography on a silca gel column eluting with 5% methanol–benzene to give 2.30 g (87%) of a 60:40 mixture of **8a** and **8b** as an oil which solidified on standing. Recrystallization from *n*-hexane–dichloromethane gave **8a** as prisms: mp 67–69°; ir (KBr) 2980, 2920, 2260, 1658, 1445, 1388, and 848 cm^{-1}; nmr ($CDCl_3$) τ 4.63 (br s, 1, C_5 H), 4.77 (br d, J = 10.0 Hz, 1, C=CH), 6.07 (br d, J = 10.0 Hz, 1, C_6 H), 6.95 (br, q, J = 7.5 Hz, 1, C_3 H), 8.13 (s, 9, C_4 CH_3 and $C(CH_3)_2$), and 8.37 (d, J = 7.5 Hz, 3, C_3 CH_3).

Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.39; H, 6.12; N, 21.49.

5,6-Dimethyl-8-isobutenyl-5,8,9,10-tetrahydro-1,4-naphthoquinone (9a) and 1,4-Dihydroxy-5,6-dimethyl-8-isobutenyl-5,8-dihydronaphthalene (10a).—The reaction product from 13.6 g (0.100 mol) of alloocimene and 10.8 g (0.100 mol) of *p*-benzoquinone was treated with *n*-hexane in order to remove insoluble quinhydrone and polymers. The soluble portion in *n*-hexane was purified by distillation to give a fraction of bp 150–168° (0.15 mm) which was chromatographed on a silica gel column eluting with chloroform to afford 3.41 g (14%) of *ca.* 7:3 mixture of **9a** and **9b** as an oil. Recrystallization of the solidified mixture from *n*-hexane–dichloromethane gave **9a** as pale green crystals: mp 81–84°; ir (KBr) 2924, 1680, 1650, 1600, 1443, and 1372 cm^{-1}; nmr ($CDCl_3$) τ 3.33 (s, 2, C_2 H and C_3 H), 4.72 (br s, 1, C_7 H), 4.84 (m, 1, C=CH), 6.58 (br m, 3, C_8 H, C_9 H, and C_{10} H), 7.53 (br m, 1, C_5 H), 8.22, 8.34 (s, 6, $C(CH_3)_2$), 8.43 (d, J = 2.0 Hz, 3, C_6 CH_3), and 8.80 (d, J = 7.5 Hz, 3, C_5 CH_3).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.49; H, 8.18.

Chromatography of **9a** on an alumina column eluting with benzene gave **10a** in 95% yield as needles from *n*-hexane–dichloromethane: mp 104.5–105.5° dec; ir (KBr) 3320, 2970, 2920, 1622, 1487, 1375, 903, 795, and 740 cm^{-1}; nmr ($CDCl_3$) τ 3.39 (s, 2, C_2 H and C_3 H), 4.42 (br m, 2, 2OH), 4.58 (br d, J = 5.0 Hz, 1, C_7 H), 4.99 (br d, J = 12.0 Hz, 1, C=CH), 5.77 (br m, 1, C_8 H), 6.55 (br q, J = 7.0 Hz, 1, C_5 H), 8.08 (m, 6, $C(CH_3)_2$), 8.23 (s, 3, C_6 CH_3), and 8.67 (d, J = 7.0 Hz, 3, C_5 CH_3).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.48; H, 8.20.

2-Phenyl-3,4-dimethyl-6-isobutenyl-3,6-dihydro-1,2-oxazine (11a) and 2-Phenyl-3-isobutenyl-5,6-dimethyl-3,6-dihydro-1,2-oxazine (12a).—The product from 9.20 g (66.7 mmol) of alloocimene and 3.60 g (33.3 mmol) of nitrosobenzene was distilled to give 4.67 g of an oil, bp 86–90° (0.05 mm), which was chromatographed on an alumina (Woelm, neutral, grade I) column eluting with *n*-hexane–benzene to give 2.63 g (32%) of **11a** and 1.31 g (16%) of **12a** both as oils successively. **11a**: $n^{19}D$ 1.5465; ir (neat) 3030, 2980, 2924, 1660, 1600, 1495, 1372, 755, and 690 cm^{-1}; nmr (CCl_4) τ 2.99 (br m, 5, C_6H_5), 4.71 (br s, 1, C_6 H), 4.93 (br s, 2, C=CH and C_5 H), 6.24 (br q, J = 7.0 Hz, 1, C_3H), 8.24 (s, 9, C_4 CH_3 and $C(CH_3)_2$), and 8.92 (d, J = 7.0 Hz, 3, C_3 CH_3); mass spectrum m/e (rel intensity) 243 (86.1), 198 (32.8), 137 (98.0), 136 (68.0), 122 (100.0), 121 (59.8), 119 (39.3), 118 (43.4), 107 (67.2), 105 (96.5), 79 (91.8), 77 (75.4), 65 (53.3), 55 (87.7), and 53 (66.4).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.49; H, 8.47; N, 6.10.

12a: $n^{19}D$ 1.5565; ir (neat) 3030, 2980, 2924, 1659, 1600, 1495, 1371, 857, 755, and 690 cm^{-1}; nmr (CCl_4) τ 3.02 (br m, 5, C_6H_5), 4.65 (br s, 2, C=CH and C_4 H), 5.12 (br m, 1, C_3 H), 6.25 (br q, J = 7.0 Hz, 1, C_6 H), 8.28 (m, 9, C_5 CH_3 and $C(CH_3)_2$), and 8.95 (d, J = 7.0 Hz, 3, C_6 CH_3); mass spectrum m/e (rel intensity) 243 (26.4), 137 (23.6), 136 (92.7), 122 (21.8), 121 (100.0), and 77 (37.3).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.59; N, 5.76. Found: C, 78.73; H, 8.59; N, 5.58.

2,3-Dimethyl-5-isobutenyl-8-phenyl-1,6,8-triazabicyclo[4.3.0]-non-3-ene-7,9-dione (13a).—The product from 2.04 g (15.0 mmol) of alloocimene and 3.50 g (20.0 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione was purified by chromatography on a silica gel column eluting with chloroform to give 3.68 g (79%) of a 75:25 mixture of **13a** and **13b** as an oil which solidified on standing. Recrystallization from *n*-hexane–dichloromethane afforded **13a** as colorless crystals: mp 100–102.5°; ir (KBr) 3020, 2924, 1767, 1706, 1600, 1505, 1420, 1380, 724, and 685 cm^{-1}; nmr ($CDCl_3$) τ 2.56 (br m, 5, C_6H_5), 4.66 (s, 1, C_5 H), 4.94 (br s, 2, C=CH and C_4 H), 5.68 (br q, J = 7.0 Hz, 1, C_2 H), 8.20 (s, 9, $C(CH_3)_2$ and C_3 CH_3), and 8.52 (d, J = 7.0 Hz, 3, C_2CH_3); mass spectrum m/e (rel intensity) 311 (2.1), 168 (43.8), 154 (41.1), 153 (31.5), 149 (24.7), 73 (100.0), and 57 (32.9).

Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.21; H, 6.75; N, 13.24.

Registry No.—**1a**, 3016-19-1; **1b**, 7216-56-0; **2a**, 28875-58-3; **3**, 28875-59-4; **4**, 28957-66-6; **5a**, 28875-60-7; **6**, 28875-61-8; **7**, 28875-62-9; **8a**, 28875-63-0 **9a**, 28875-64-1; **10a**, 28875-65-2; **11a**, 28875-66-3 **12a**, 28875-67-4; **13a**, 28875-68-5.

Photochemical Cycloadditions of 1,3-Dipolar Systems. I. Additions of *N,C*-Diphenylsydnone and 2,5-Diphenyltetrazole

C. S. Angadiyavar and M. V. George*[1]

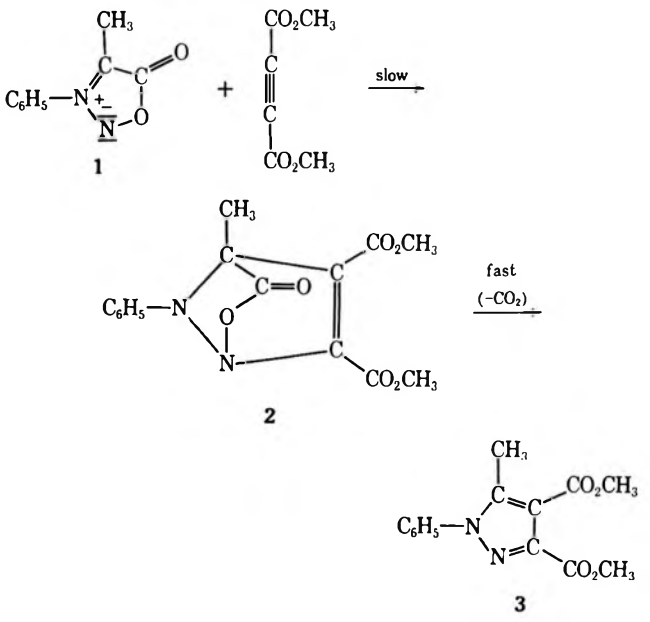
Department of Chemistry, Indian Institute of Technology, Kanpur, India

Received April 1, 1970

Photochemical cycloaddition of *N,C*-diphenylsydnone to dimethyl acetylenedicarboxylate gives rise to dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate, different from the thermal addition product. Similarly, the photoaddition of *N,C*-diphenylsydnone to dimethyl fumarate and dimethyl maleate gives rise to a mixture of dimethyl 1,3-diphenylpyrazoline-*trans*-4,5-dicarboxylate and dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate in each case. The photochemical transformation of *N,C*-diphenylsydnone, in the absence of any dipolarophile, leads to a mixture of benzil osazone, 2,4,5-triphenyl-1,2,3-triazole, and benzanilide. It has been suggested that the photoreactions of *N,C*-diphenylsydnone proceed through the intermediate formation of *N,C*-diphenylnitrileimine which then adds to the external dipolarophiles giving rise to the observed products. *N,C*-Diphenylnitrileimine has also been postulated as the intermediate in the photochemical cycloadditions of 2,5-diphenyltetrazole. Photolysis of 2,5-diphenyltetrazole in the absence of any added dipolarophile gives rise to a mixture of 2,4,5-triphenyl-1,2,3-triazole and benzil osazone.

Sydnones form a class of mesoionic compounds which contain the azomethineimine system as part of an aromatic ring.[2] In spite of their aromaticity, sydnones behave as potential 1,3-dipolar systems, undergoing addition reactions with different dipolarophiles.[3] These reactions, in general, are thermally induced, concerted processes which are allowed on the basis of orbital symmetry considerations.[4,5] In the reaction of *C*-methyl-*N*-phenylsydnone (**1**) with dimethyl acetylenedicarboxylate, for example, a nearly quantitative yield of dimethyl 5-methyl-1-phenylpyrazole-3,4-dicarboxylate (**3**) is formed. It has been suggested,[3g] on the basis of kinetic studies, that this reaction proceeds through the initial formation of an intermediate **2**, in a slow, rate-determining step, followed by a rapid loss of carbon dioxide from **2** to give the pyrazole **3** (Scheme I). The object of the present work was to study the photochemical cycloadditions of a cyclic azomethineimine, such as *N,C*-diphenylsydnone, with a view to examining the nature of the products formed in these reactions.

Scheme I



Irradiation of a mixture of *N,C*-diphenylsydnone (**4**) and dimethyl acetylenedicarboxylate in benzene solution for 2 hr gave a 67% yield of dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (**9**). The identity of this product was confirmed through an independent synthesis by a reported procedure.[6] It is pertinent to observe that the pyrazoles formed from the reaction of **4** with dimethyl acetylenedicarboxylate in thermal and photochemical reactions are not identical; the photoreaction leads to the formation of the pyrazole **9**, whereas dimethyl 1,5-diphenylpyrazole-3,4-dicarboxylate (**11**) is formed under thermal conditions. The possibility of photoisomerization of the pyrazole **11** to **9** under our reaction conditions was ruled out by showing, in a separate experiment, that **11** does not undergo photochemical isomerization when irradiated in benzene solution for a longer period (6 hr) than the time employed for the photochemical cycloaddition of **4** with dimethyl acetylenedicarboxylate.

A plausible route to the formation of **9** in the photoaddition of **4** is shown in Scheme II. In this scheme we assume that the first step in the reaction is the photochemical transformation of the starting sydnone **4** to an intermediate **5** (corresponding to the earlier structure suggested by Earl and Mackney for sydnone).[7] The intermediate **5** can then lose carbon dioxide to give the diazirine derivative **6**, which in turn would lead to *N,C*-diphenylnitrileimine (**7**), through a ring-opening process. Alternatively, the sydnone **4** can directly lose carbon dioxide under photolytic conditions to give the carbenonitrene intermediate **8**, which can then rearrange to *N,C*-diphenylnitrileimine. The nitrileimine **7** can subsequently react with dimethyl acetylenecarboxylate either through a thermal or a photochemical pathway to give the pyrazole **9**. In this connection, it might be mentioned that *N*-phenylnitrileimine has also been suggested as an intermediate

(1) To whom all inquiries should be addressed.

(2) For comprehensive reviews on sydnones, see (a) W. Baker and W. D. Ollis, *Quart. Rev. (London)*, **11**, 15 (1957); (b) F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964).

(3) For some of these additions, see (a) H. Gotthardt, Ph.D. Thesis, München, 1964; (b) R. Huisgen, R. Grashey, H. Gotthardt, and R. Schmidt, *Angew. Chem. Int. Ed. Engl.*, **1**, 48 (1962); (c) R. Huisgen, H. Gotthardt, and R. Grashey, *ibid.*, **1**, 49 (1962); (d) H. Gotthardt and R. Huisgen, *Chem. Ber.*, **101**, 839 (1968); (f) H. Gotthardt, R. Huisgen, and R. Knorr, *ibid.*, **101**, 1056 (1968); (g) R. Huisgen and H. Gotthardt, *ibid.*, **101**, 1059 (1968).

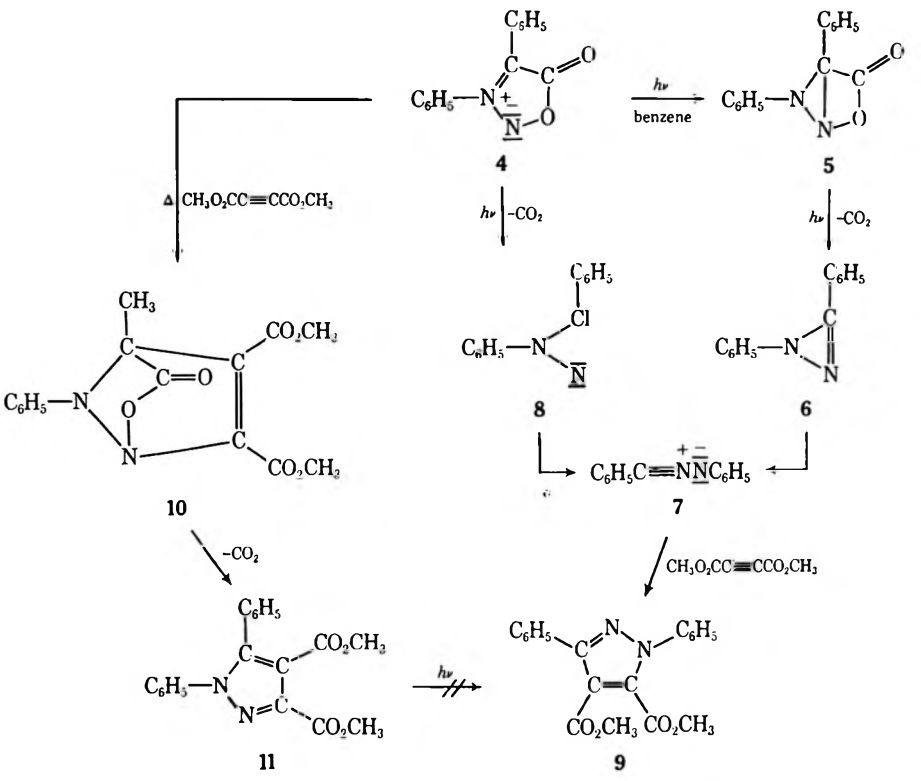
(4) (a) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968); (b) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968); (c) R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).

(5) R. Huisgen, *ibid.*, **2**, 633 (1963).

(6) R. Huisgen, M. Seidel, G. Wallbilich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).

(7) J. C. Earl and A. W. Mackney, *J. Chem. Soc.*, 899 (1935).

SCHEME II

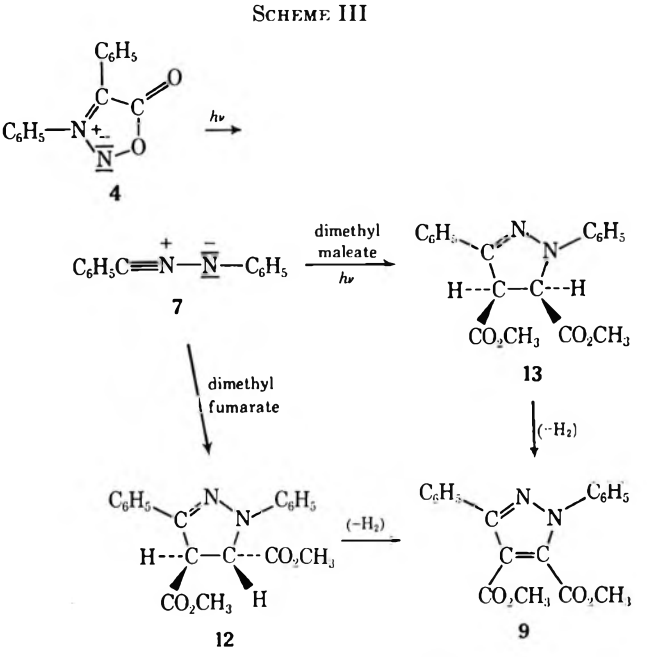


in the photochemical transformation of *N*-phenylsydnone to 3-phenyloxa-3,4-diazolinone-2.[8] We therefore felt it necessary to examine in detail some of the photochemical additions of **4** and related systems with a view to studying the nature of the products formed in these reactions.

Irradiation of a 1:1 mixture of **4** and dimethyl fumarate in benzene for 2 hr gave a 28% yield of dimethyl 1,3-diphenylpyrazoline-*trans*-4,5-dicarboxylate (**12**) together with a small quantity (6%) or the dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (**9**). An increased yield of the pyrazoline **12** (52%) was obtained when the photoaddition was carried out using a 1:2 mixture of **4** and dimethyl fumarate. The formation of small amounts of pyrazole **9** can be rationalized in terms of a possible dehydrogenation of **12** by dimethyl fumarate, under the reaction conditions. The actual occurrence of such a dehydrogenation reaction has been verified by irradiating a mixture of the pyrazoline **12** and dimethyl fumarate in benzene solution, when a 24% yield of the pyrazole **9** was obtained.

Similarly, the photoreaction of a 1:1 mixture of **4** and dimethyl maleate gave a 20% yield of the *trans*-pyrazoline **12** and a 27% yield of the pyrazole **9**. A probable route to the formation of **9** is through the dehydrogenation of the pyrazoline **12** or dimethyl 1,3-diphenylpyrazoline-*cis*-4,5-dicarboxylate (**13**), the expected product of the stereospecific addition of **7** to dimethyl maleate (Scheme III). The formation of the *trans*-pyrazoline **12** from the reaction of **4** with dimethyl maleate, however, may be explained in terms of the photoisomerization of dimethyl maleate[9] to

SCHEME III



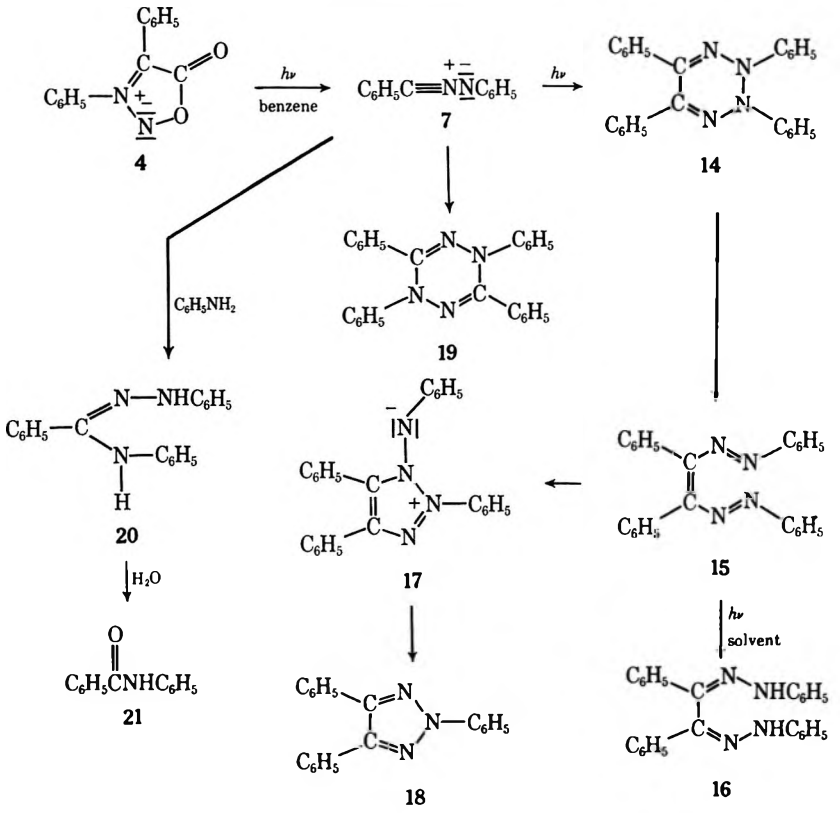
dimethyl fumarate which could then combine with the nitrileimine **7**.

If *N*,*C*-diphenylnitrileimine (**7**) is involved as an intermediate in the photochemical addition of **4**, as shown in Scheme II, then it would be reasonable to assume that the photolysis of **4** in the absence of any dipolarophile should give rise to products which are essentially those derived from **7**. Irradiation of a benzene solution of **4** for 2 hr led to the formation of a mixture of products consisting of benzil osazone (**16**, 3%), 2,4,5-triphenyl-1,2,3-triazole (**18**, 14%), and benzanilide (**21**, 3%). A probable route to the formation of these products is shown in Scheme IV. In

(8) C. H. Krauch, J. Kuhls, and H. J. Piek, *Tetrahedron Lett.*, 4043 (1966).

(9) For some photosensitized isomerizations of diethyl maleate and diethyl fumarate, see G. S. Hammond, J. Saltiel, A. A. Lamole, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Amer. Chem. Soc.*, **86**, 3197 (1964).

SCHEME IV



this scheme we assume that the nitrileimine **7**, formed from **4**, undergoes a photochemical cycloaddition to give 2,3,5,6-tetraphenyl-2,3-dihydro-1,2,3,4-tetrazine (**14**). A nitrileimine such as **7** is essentially a four-electron system (those involved in addition reactions) and therefore its photochemical dimerization to give **14** would be an allowed 4 + 4 addition reaction.[4] The thermal dimerization of **7** is reported to give rise to 2,3,5,6-tetraphenyl-2,5-dihydro-1,2,4,5-tetrazine (**19**)[10] and this reaction in all probability may be proceeding by a nonconcerted process. The dihydrotetrazine **14** can then undergo ring opening either thermally or photochemically to give the bisazoethylene derivative **15**, which in turn can exist in the zwitterionic from **17**.[11,12] This intermediate **17** can then be converted to 2,4,5-triphenyl-1,2,3-triazole (**18**), either thermally or photochemically through the loss of phenylnitrene. The exact mode of formation of benzil osazone (**16**) is not very clear. However, it might arise through a free-radical process involving the hydrogen abstraction from the solvent of a possible diradical species generated from either **14** or **15**, under photochemical conditions. The formation of small amounts of benzanilide (**21**) can be explained in terms of the reaction of aniline, one of the possible side products in this reaction, with the nitrileimine **7** to give *N*-phenylbenzanilide phenylhydrazone (**20**)[10] which may undergo hydrolysis either during the reaction or work-up.

A second possible route to the formation of the triazole **18** is through the reaction of the nitrileimine **7** with benzonitrile which could arise from the fragmentation of **7**. The fact that there was not any appreciable increase in the yield of the triazole **18**, when the photolysis of **4** was carried out in presence of benzonitrile, strongly suggests that the triazole formation may not be taking place through this route, in the photolysis of the sydnone **4**.

Our next objective was to study the thermal and photochemical transformations of the dihydrotetrazine **14** which have been postulated as intermediates in the sequence of reactions shown in Scheme IV. Photolysis of **14** in benzene solution for 2 hr led to the formation of a 14% yield of 2,4,5-triphenyl-1,2,3-triazole (**18**) and 2% yield of benzil osazone (**16**).[13] It is therefore reasonable to assume that both the triazole **18** and benzil osazone (**16**) are formed through the dihydrotetrazine **14** in the photolysis of *N,C*-diphenylsydnone. In this connection, it might be mentioned that the triazole **18** is formed in a 85% yield on heating the dihydrotetrazine alone for about 15 min around 175°. The thermal transformation of **14** may also be taking place through the intermediates **15** and **17**, as shown in Scheme IV.

With a view to finding out whether 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine (**19**) is involved as an intermediate in the formation of either the triazole **18** or benzil osazone (**16**) in the photolysis of **4**, we have examined the photolysis of this dihydrotetrazine also. When **19** was photolyzed in benzene solution for 3 hr, practically no change occurred and most of the material was recovered unchanged. The fact that **19** is not undergoing any further transformation

(10) R. Huisgen, J. Sauer, and M. Seidel, *Chem. Ber.*, **94**, 2503 (1961).

(11) For a similar zwitterionic repesentation of the oxidation product of dibenzoyloxazone of biacetyl, see S. Petersen and H. Heitzer, *Angew. Chem. Int. Ed. Engl.*, **9**, 67 (1970).

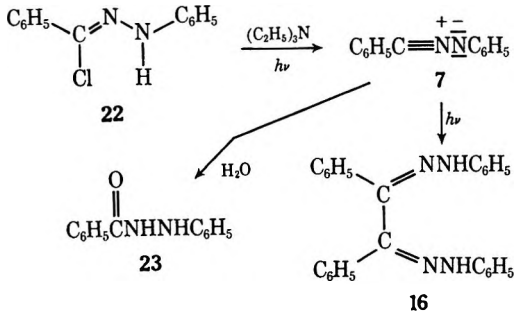
(12) For some of the 1,3-dipolar cycloaddition reactions of **17**, see C. S. Angadiyavar, K. B. Sukumaran, and M. V. George, *Tetrahedron Lett.*, 633 (1971).

(13) On completion of our studies, we came across a recent report concerning the formation of the triazole **18** from the bisazoethylene **15** [C. Wintner, *ibid.*, 2275 (1970)].

suggests that it is not being formed as an intermediate in the photolysis of **4**.

If the triazole **18** and benzil osazone (**16**) are formed from **7** in the photolysis of **4**, then it would be reasonable to assume that the nitrileimine **7**, generated by other methods, should also be capable of undergoing a photochemical transformation leading to the same products. In this connection, we have attempted the photolysis of **7** generated *in situ* by treatment of triethylamine with α-chlorobenzaldehyde phenylhydrazone (**22**).[6] From this reaction, however, the only products that could be isolated were a trace of benzil osazone and a 19% yield of benzoylphenylhydrazide (**23**) (Scheme V).

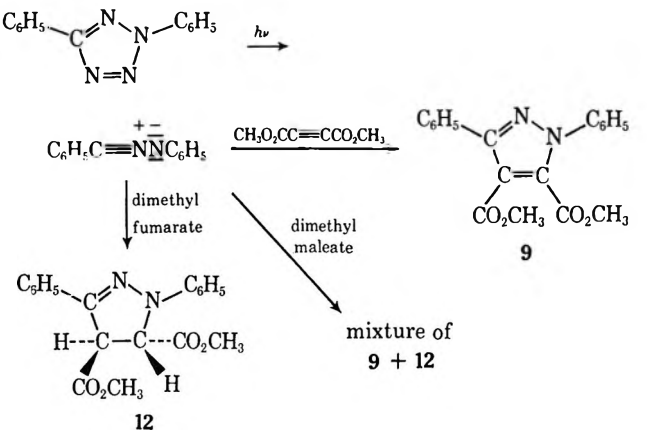
SCHEME V



The formation of **23** could be explained in terms of the reaction of the nitrileimine **7** with water during the course of the reaction or work-up. It has been reported[14] that triethylamine itself undergoes photolysis to give a mixture of the meso and racemic forms of 2,3-bisdiethylaminobutane and this complicating side reaction may be responsible for the poor yield of the desired products. It was then felt necessary to study the photolysis of the nitrileimine intermediate **7** in the absence of other reagents which might interfere with the desired reaction.

The thermal decomposition of tetrazoles are reported to give rise to a variety of products and it has been suggested that nitrileimines are involved as intermediates in some of these reactions.[15] It would be reasonable to expect that nitrileimines are also involved in the photochemical decompositions of tetrazoles. The observation that a mixture of isomeric pyrazolines are formed in the photochemical reaction between 2,5-diphenyltetrazole (**24**) and methyl crotonate strongly suggests that *N,C*-diphenylnitrileimine is involved as an intermediate in this reaction.[15c] Further, we find that 2,5-diphenyltetrazole (**24**) undergoes photochemical cycloaddition with different dipolarophiles leading to products which are identical with those obtained from the thermal reactions of *N,C*-diphenylnitrileimine with these dipolarophiles. Thus, in the photolysis of a mixture of **24** and dimethyl acetylenedicarboxylate, a 81% yield of the pyrazole **9** is obtained. Similarly, the photoreaction of **24** with dimethyl fumarate gives rise to a 73% yield of the *trans*-pyrazoline **12**. The photochemical reaction between **24** and dimethyl maleate, on the other hand, leads to a mixture of the pyrazoline **12** and pyrazole **9**. The formation of these products could be rationalized in terms of the reactions of the nitrileimine **7**, as shown in Scheme VI. The

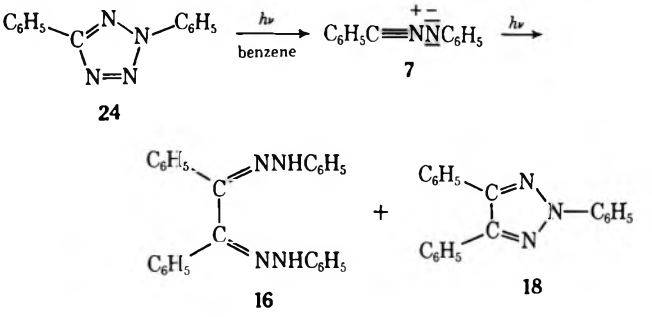
SCHEME VI



recent report on the photochemical cycloaddition reaction of 3,4-diphenyl-Δ²-1,2,4-oxazolinone-5 with various dipolarophiles may also be explained in terms of the reaction of *N,C*-diphenylnitrileimine, a possible intermediate in this reaction.[16]

If *N,C*-diphenylnitrileimine (**7**) is formed as an intermediate in the photolysis of 2,5-diphenyltetrazole (**24**), then one would expect that the photolysis of **24** in the absence of any dipolarophile to give rise to products identical with those formed in the photolysis of *N,C*-diphenylsydnone. Irradiation of a benzene solution of **24** for 1.5 hr gave a 28% yield of the triazole **18** and a 3% yield of benzil osazone (**16**) (Scheme VII).

SCHEME VII



The formation of products such as **16** and **18** in the photolysis of **24** can be rationalized in terms of the nitrileimine intermediate **7**, as shown in Scheme IV. It might be mentioned in this connection that Fraser and coworkers have recently reported that the photolysis of 2-methyl-5-phenyltetrazole in dioxane medium gives rise to a mixture of products consisting of 2-methyl-4,5-diphenyl-1,2,3-triazole, 1,2-di(methylazo)-1,2-diphenylethylene, and 1-methyl-3,5-diphenyl-1,2,4-triazole.[17a] These authors have suggested that the starting material undergoes an initial 2 + 2 addition to give a dimeric product which then decomposes through the loss of nitrogen and methyl azide to give

(14) K. Pfordte and G. Leuschner, *Justus Liebigs Ann. Chem.*, **646**, 25 (1961).

(15) For some of the thermal decomposition of tetrazoles, see (a) R. Huisgen, J. Sauer, and M. Seidel, *ibid.*, **654**, 146 (1962); (b) J. H. Markgraf, S. H. Brown, M. W. Kaplinsky, and R. G. Peterson, *J. Org. Chem.*, **29**, 2629 (1964); (c) J. S. Clovis, A. Eckell, R. Huisgen, and R. Sustmann, *Chem. Ber.*, **100**, 60 (1967).

(16) J. Sauer and K. K. Mayer, *Tetrahedron Lett.*, 325 (1968).

(17) (a) R. R. Fraser, Gurudatta, and K. E. Haque, *J. Org. Chem.*, **34**, 4118 (1969). (b) On completion of our work we became aware of a recent report on the photolysis of 2,5-diphenyltetrazole [*P.* Scheiner and J. F. Dinda, Jr., *Tetrahedron*, **26**, 2619 (1970)] wherein a similar 2 + 2 cycloaddition has been postulated.

the observed products.[17b] The ease with which tetrazoles lose nitrogen, and also undergo photochemical cycloaddition in the presence of dipolarophiles, would suggest that the dimerization of tetrazoles through a 2 + 2 addition may not be the only path to be considered under these conditions.

Experimental Section

All melting points are uncorrected. All irradiation experiments were carried out using a Hanovia medium-pressure mercury lamp (450 W).

Starting Materials.—*N,C*-Diphenylsydnone,[18] mp 185° (56%), 2,5-diphenyltetrazole,[19] mp 102° (68%), 2,3,5,6-tetraphenyl-2,3-dihydro-1,2,3,4-tetrazine,[20] mp 170° (54%), and 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine,[21] mp 204° (26%), were prepared by reported procedures. Benzene used for photolysis was purified by standard procedures and dried over sodium.

Photochemical Reaction of *N,C*-Diphenylsydnone with Dimethyl Acetylenedicarboxylate.—A mixture of 0.48 g (0.002 mol) of *N,C*-diphenylsydnone and 0.57 g (0.004 mol) of dimethyl acetylenedicarboxylate was irradiated in benzene solution (175 ml) for 2 hr. Removal of the solvent under vacuum gave a product which on treatment with a small portion of ethanol gave 0.45 g (67%) of dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate (9) which melted at 156° after recrystallization from ethanol. There was no depression in the melting point of 9 when mixed with an authentic sample.[6]

Attempted Photochemical Isomerization of Dimethyl 1,5-Diphenylpyrazole-3,4-dicarboxylate (11).—A solution (175 ml) of the pyrazole 11 (0.5 g, 0.0016 mol) in benzene was irradiated for 6 hr. Removal of the solvent under vacuum gave a product which on fractional crystallization from ethanol gave 0.49 g (98%) of the unchanged starting pyrazole 11, mp 98–99° (mmp).

Photochemical Reaction of *N,C*-Diphenylsydnone with Dimethyl Fumarate.—Irradiation of a benzene solution (175 ml) of a mixture of 4 (0.48 g, 0.002 mol) and dimethyl fumarate (0.29 g, 0.002 mol) for 2 hr and removal of the solvent under vacuum gave a residue which on fractional crystallization from methanol gave 0.19 g (28%) of dimethyl 1,3-diphenylpyrazoline-*trans*-4,5-dicarboxylate (12), mp 154° (mmp). From the mother liquor was isolated 50 mg (6%) of 9, mp 156° (mmp).

In a repeat run, 0.48 g (0.002 mol) of 4 was irradiated with 0.58 g (0.004 mol) of dimethyl fumarate in 175 ml of benzene for 2 hr to give 0.35 g (52%) of 12, mp 154° (mmp).

Photochemical Reaction of *N,C*-Diphenylsydnone with Dimethyl Maleate.—A benzene solution (175 ml) of a mixture of 4 (0.48 g, 0.002 mol) and dimethyl maleate (0.29 g, 0.002 mol) was irradiated for 2 hr. Removal of the solvent under vacuum gave a solid which on fractional crystallization from methanol gave a 20% yield (0.14 g) of 12, mp 154° (mmp). From the mother liquor was isolated 27% (0.18 g) of 9, mp 156° (mmp).

Photochemical Dehydrogenation of 12 Using Dimethyl Maleate.—A benzene solution (175 ml) of a mixture of 0.34 g (0.001 mol) of 12 and 0.44 g (0.005 mol) of dimethyl maleate was irradiated for 2 hr. Removal of the solvent gave a residue which was fractionally crystallized from methanol to give 0.16 g (47%) of 9, mp 156° (mmp), and 0.13 g (38%) of unchanged starting material 12, mp 154° (mmp).

Photochemical Dehydrogenation of 12 Using Dimethyl Fumarate.—A mixture of 0.34 g (0.001 mol) of 12 and 0.44 g (0.003 mol) of dimethyl maleate in 175 ml of benzene was irradiated for 2 hr. Work-up of the mixture as in the earlier case gave 0.08 g (24%) of 9, mp 156° (mmp), and 0.19 g (56%) of unchanged starting material 12, mp 154° (mmp).

Photochemical Isomerizations of Dimethyl Maleate and Dimethyl Fumarate.—Irradiation of a solution of 0.57 g (0.004 mol) of dimethyl maleate in benzene (175 ml) for 2 hr and work-up in the usual manner gave 0.14 g (24%) of dimethyl fumarate, mp 104° (mmp), and 0.38 g (67%) of unchanged dimethyl maleate, bp 201°.

In a similar run, irradiation of a benzene solution (175 ml) of dimethyl fumarate (0.57 g, 0.004 mol) for 2 hr resulted in the isolation of a 63% yield (0.36 g) of dimethyl maleate, bp 201° and 18% (0.1 g) unchanged dimethyl fumarate, mp 104° (mmp).

Photolysis of *N,C*-Diphenylsydnone.—A solution of 0.48 g (0.002 mol) of 4 in benzene (175 ml) was irradiated for 2 hr. Removal of the solvent under vacuum gave a product which was chromatographed on alumina. Elution with petroleum ether (bp 60–80°) gave 0.04 g (14%) of 2,4,5-triphenyl-1,2,3-triazole (18) which melted at 124° after recrystallization from petroleum ether (bp 60–80°). There was no depression in the melting point of 18 when mixed with an authentic sample.[22]

Further elution of the alumina column with a mixture (3:1) of petroleum ether (bp 60–80°) and benzene gave 0.01 g (3%) of benzil osazone (16), mp 234° (mmp). Subsequent elution of the column with benzene gave 0.01 g (3%) of benzanilide (21), mp 167° (mmp).

Photolysis of 2,3,5,6-Tetraphenyl-2,3-dihydro-1,2,3,4-tetrazine (14).—A solution of 0.39 g (0.001 mol) of 14 in 175 ml of benzene was irradiated for 2 hr. Removal of the solvent under vacuum gave a product which was chromatographed on alumina. Elution with petroleum ether (bp 60–80°) gave 0.04 g (14%) of 2,4,5-triphenyl-1,2,3-triazole (18), mp and mmp 124°. Further elution of the column with a mixture (3:1) of petroleum ether and benzene gave 6 mg (2%) of benzil osazone, mp and mmp 154°.

Thermal Decomposition of 2,3,5,6-Tetraphenyl-2,3-dihydro-1,2,3,4-tetrazine (14).—The dihydrotetrazine 14 (0.2 g, 0.5 mmol) was heated in a sealed tube around 175–180° in an oil bath for 15 min and the product mixture was chromatographed on alumina. Elution with petroleum ether (bp 60–80°) gave 0.13 g (85%) of the triazole 18, mp 124° (mmp).

Attempted Photolysis of 1,3,4,6-Tetraphenyl-1,4-dihydro-1,2,-4,5-tetrazine (19).—A solution of 0.4 g (0.001 mol) of 19 in 175 ml of benzene was photolyzed for 3 hr. Removal of the solvent under vacuum and work-up as in the previous case gave 0.39 g (96%) of the starting material, mp 204° (mmp).

Photolysis of *N,C*-Diphenylnitrileimine (7) **Generated from α-Chlorobenzaldehyde Phenylhydrazone.**—A solution of triethylamine (1 g, 0.01 mol) in benzene (20 ml) was gradually added to a benzene solution (150 ml) of α-chlorobenzaldehyde phenylhydrazone[6] (0.46 g, 0.002 mol), kept inside the photochemical reactor. The addition was completed in about 30 min, but the irradiation was continued for a further period of 2 hr. Removal of the solvent under vacuum gave a product which was chromatographed on alumina. Elution of the column with a mixture (3:1) of petroleum ether (bp 60–80°) and benzene gave a trace of benzil osazone identified on a tlc plate by comparison with an authentic sample. Further elution of the column with a mixture (3:1) of benzene and ethyl acetate gave 0.08 g (19%) of benzoylphenylhydrazine, mp and mmp 172° (lit.[23] mp 168°).

Photochemical Reaction of 2,5-Diphenyltetrazole with Dimethyl Acetylenedicarboxylate.—A mixture of 0.45 g (0.002 mol) of 2,5-diphenyltetrazole and 0.43 g (0.002 mol) of dimethyl acetylenedicarboxylate was irradiated in benzene solution (175 ml) for 2 hr. Removal of the solvent under vacuum gave a product which on treatment with a small amount of ethanol gave 0.55 g (81%) of dimethyl 1,3-diphenylpyrazole-4,5-dicarboxylate which melted at 156° after recrystallization from ethanol. There was no depression in the melting point on admixture with an authentic sample.[6]

Photochemical Reaction of 2,5-Diphenyltetrazole with Dimethyl Fumarate.—Irradiation of a mixture of 0.45 g (0.002 mol) of the tetrazole 24 and 0.29 g (0.002 mol) of dimethyl fumarate in benzene solution (175 ml) for 1.5 hr and work-up as in the previous case gave 0.48 g (73%) of dimethyl 1,3-diphenyl-*trans*-pyrazoline-4,5-dicarboxylate, mp 154° (mmp).

Photochemical Reaction of 2,5-Diphenyltetrazole with Dimethyl Maleate.—A benzene solution (175 ml) of a mixture of 2,5-diphenyltetrazole (0.45 g, 0.002 mol) and dimethyl maleate (0.29 g, 0.002 mol) was irradiated for 1.5 hr. Removal of the solvent gave a mixture of products which was fractionally crystallized from methanol to give 0.27 g (40%) of the *trans*-pyrazoline 12, mp 154° (mmp), and 55 mg (8%) of the pyrazole 9, mp 156° (mmp).

Photolysis of 2,5-Diphenyltetrazole.—A solution of 0.45 g (0.002 mol) of the tetrazole 24 in 175 ml of benzene was irradiated for 1.5 hr. Removal of the solvent under vacuum gave a mixture

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of products which was chromatographed on alumina. Elution with petroleum ether (bp 60–80°) gave 80 mg (28%) of 2,4,5-triphenyl-1,2,3-triazole (18), mp 124° (mmp). Further elution of the column with a mixture (3:1) of petroleum ether and benzene gave 10 mg (3%) of benzil osazone, mp 234° (mmp). No other product could be isolated from this run.

Registry No.—4, 28638-85-9; 7, 834-27-5; 12, 17679-79-7; 14, 28595-91-7; 24, 18039-45-7; dimethyl acetylenedicarboxylate, 762-42-5; dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6.

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A New Synthesis of 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA Riboside) *via* the Reduction of 1-(β-D-Ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DIC Riboside)[1]

RAYMOND P. PANZICA[2] AND LEROY B. TOWNSEND*

Department of Chemistry and Department of Biopharmaceutical Sciences, University of Utah, Salt Lake City, Utah 84112

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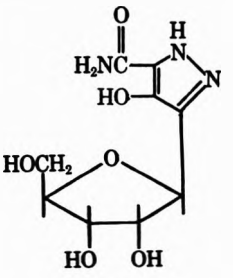
1-(β-D-Ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (5, DIC riboside) and 1-(β-D-ribofuranosyl)-4-(3,3-dimethyl-1-triazeno)imidazole-5-carboxamide (6, iso-DIC riboside) have been synthesized by the direct ribosidation of the trimethylsilyl derivative of 5(4)-(3,3-dimethyl-1-triazeno)imidazole-4(5)-carboxamide (DIC). The assignment of anomeric configuration and proof for the site of glycosidation of these nucleosides (5 and 6) were achieved by catalytic cleavage of the –N=N– double bond to afford the imidazole nucleosides 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (7) and 4-amino-1-(β-D-ribofuranosyl)imidazole-5-carboxamide (8) of established structure.

The isolation and characterization[3] of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside) from the culture medium of sulfonamide-inhibited *E. coli* was followed by the enzymatic conversion of AICA riboside to 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide 5′-phosphate (AICAR).[4] The synthesis of AICA riboside was subsequently accomplished by ring opening of certain purine nucleosides,[5] fermentation,[6] and direct ribosidation of an imidazole derivative followed by functional group transformations.[7] A renewed interest in the chemical synthesis of AICA riboside and related derivatives has been prompted by the report[6] that AICA riboside can function effectively as a substrate for a kinase which results in a facile conversion of AICA riboside to AICAR.[8] Also of considerable interest is the recent isolation and characterization of pyrazomycin[9] as a five-membered heterocyclic riboside which is structurally very similar to AICA riboside. Previous investigations from our laboratory[10–13] on the direct glycosidation of various imidazole derivatives by the fusion procedure have usually resulted in the successful isolation of only one isomer. However, after the appropriate functional group transformations had been accomplished, the actual site of glycosidation was established as being at the ring nitrogen adjacent to the carboxamide group (iso-AICA riboside and derivatives) rather than the ring nitrogen adjacent to the exocyclic amino group (AICA riboside and derivatives) by ring annulation to afford 7-ribosylpurines. We now wish to report a convenient synthesis of both isomers (AICA riboside and iso-AICA riboside).



pyrazomycin

5(4)-(3,3-Dimethyl-1-triazeno)imidazole-4(5)-carboxamide (DIC)[14] was treated with hexamethyldisilazane to afford the trimethylsilyl derivative 1 which was then condensed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile. This procedure furnished two major components (3, 17.4%; 4, 32.2%) which were separated by column chromatography. 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4-(3,3-dimethyl-

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(2) The recipient of a University of Utah Research Committee Fellowship, 1968–1970.

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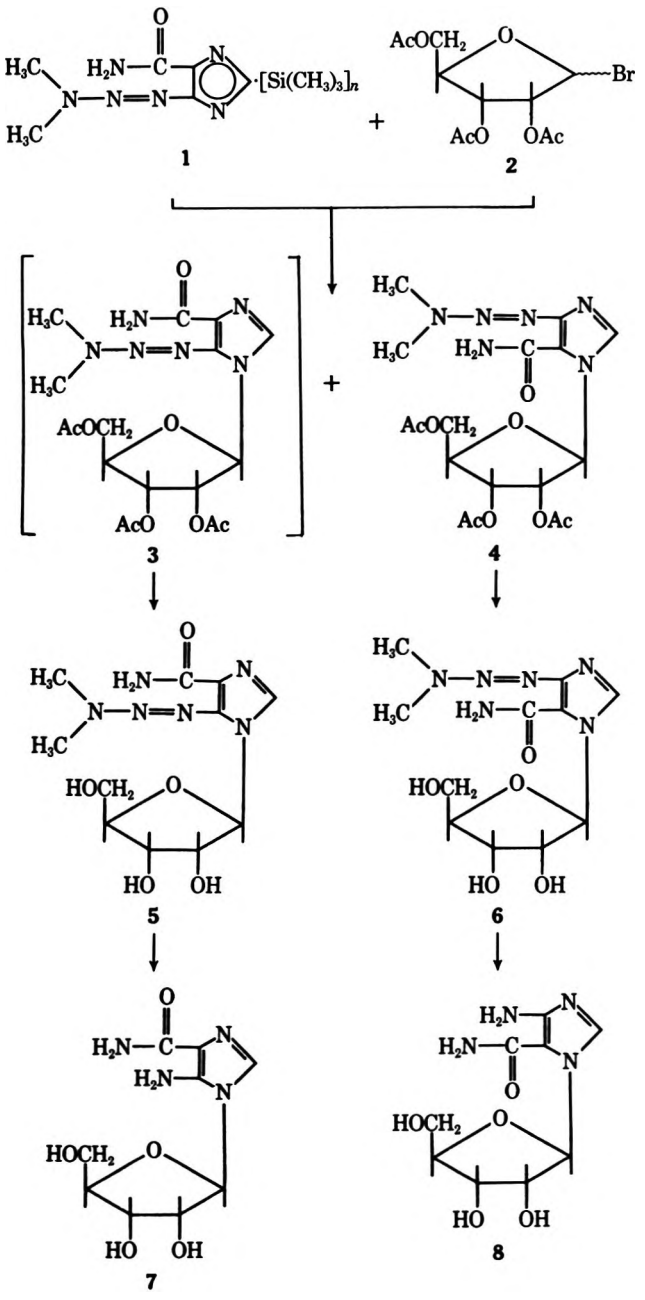
(14) The abbreviations used are DIC, 5(4)-(3,3-dimethyl-1-triazeno)-imidazole-4(5)-carboxamide, NSC-45388; AIC, 4(5)-aminoimidazole-5(4)-carboxamide; AICA riboside, 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide; iso-AICA riboside, 4-amino-1-(β-D-ribofuranosyl)imidazole-5-carboxamide; AICAR, 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide 5′-phosphate.

1-triazeno)imidazole-5-carboxamide (**4**) was crystallized from ethanol, whereas efforts to crystallize **3** (hard foam) from a variety of solvents proved fruitless. Removal of the acetyl groups from **4** by liquid ammonia (24 hr)[15] or methanolic ammonia (16 hr)[13] provided a mixture of **6** and a partially deacetylated product. However, it was found that deacetylation of **4** with methanolic ammonia (4 days) furnished 1-(β-D-ribofuranosyl)-4-(3,3-dimethyl-1-triazeno)imidazole-5-carboxamide (**6**) in 95% yield as the only product. The same conditions were used to obtain **5** by deacetylation of **3** (Scheme I).

SCHEME I



That complete deacetylation had occurred under these conditions was established by elemental analysis and pmr spectroscopy (DMSO-d_6) obtained for both **5** and **6**. A feature common to the spectra of both nucleosides is the very broad resonance (singlet, 6 protons) centered at δ 3.36 for the $N(CH_3)_2$ protons. A 100-MHz spectra of **6** (DMSO-d_6–D_2O) revealed that the *N*-methyl resonances could be separated into two broad singlets (one centered at δ 3.58, the other at δ 3.22) which indicates at least some magnetic nonequivalence for the methyl groups.

It has been demonstrated that 5(4)-(3,3-dimethyl-1-triazeno)imidazole-4(5)-carboxamide (DIC) possesses significant antitumor activity.[16-18] However, the potential of this AIC analog has been limited because of its instability toward light and heat.[19,20] Unlike DIC, the ribosides 1-(β-D-ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (**5**) (DIC riboside) and 1-(β-D-ribofuranosyl)-4-(3,3-dimethyl-1-triazeno)-imidazole-5-carboxamide (**6**) (iso-DIC riboside) have shown remarkable stability toward these factors. Solutions of **5** and **6** when exposed to direct sunlight for a period of 4 days exhibited no appreciable degradation or decomposition (tlc, uv).[19] In addition, **6** was also exposed to long-wave uv light (366 nm) for 18 hr without observing any of the effects reported[20] for DIC under similar conditions.

The assignment of anomeric configuration and site of ribosidation was established unequivocally by the reduction and cleavage of the –N=N– double bond. Treatment of an aqueous ammonical solution of **5** with Raney nickel as the catalyst in a hydrogen atmosphere afforded a product in 81% yield which was chromatographically homogeneous.[21] A comparison (ir, uv,[3] and optical rotation)[6] of this product with an authentic sample of AICA riboside[22] showed them to be identical.[23] This same procedure using **6** has provided nucleoside material in 71% yield which was established by ir, uv, and optical rotation comparisons to be iso-AICA riboside (**8**).[21] This study has furnished a new synthetic route for the preparation of AICA riboside.[5] The preparation of additional triazenoimidazole ribosides *via* the silylation procedure is under active investigation in this laboratory.

R_f values of **4**–**8** are given Table I.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The proton magnetic resonance spectra were obtained on Varian A-60 and XL-100 spectrometers utilizing DSS as an internal standard. The infrared spectra were determined in pressed potassium bromide disks with a Beckman IR-8 spectrophotometer. The ultraviolet absorption spectra were recorded on a Beckman DK-2 spectrophotometer. The optical rotations were obtained with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Silica gel suitable for chromatographic use was purchased from J. T.

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(21) Other methods such as 5% palladium on charcoal and sodium dithionite failed.

(22) Purchased from Cyclochemical Co., Los Angeles, Calif. [mp 214–215°, $[\alpha]^{21}D$ −63.7 (c 0.5, H_2O)].

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TABLE I

R_f VALUES OF CERTAIN IMIDAZOLE NUCLEOSIDES[a,b]

No.	Compd	Chromatographic solvent systems[c] A	B	C	D	E
4	1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4-(3,3-dimethyl-1-triazeno)imidazole-5-carboxamide	0.71	0.84	0.76	0.87	0.90
5	1-(β-D-Ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide	0.77	0.05	0.62	0.59	0.04
6	1-(β-D-Ribofuranosyl)-4-(3,3-dimethyl-1-triazeno)imidazole-5-carboxamide	0.64	0.17	0.72	0.70	0.21
7	5-Amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (AICA riboside)	0.67	0.07	0.54	0.54	0.10
	5-Amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide[d]	0.66	0.07	0.54	0.54	0.10
8	4-Amino-1-(β-D-ribofuranosyl)-imidazole-5-carboxamide (iso-AICA riboside)	0.74	0.06	0.48	0.55	0.07
	4-Amino-1-(β-D-ribofuranosyl)-imidazole-5-carboxamide[e]	0.73	0.06	0.49	0.55	0.07

[a] All compounds were run on Whatman No. 1 chromatographic paper and the descending technique was used. [b] Short-wave ultraviolet light (254 nm) was used to detect the spots. [c] Chromatographic solvent systems: A, 5% aqueous ammonium bicarbonate (w/w); B, 1-butanol saturated with water; C, 1-propanol–ammonium hydroxide (sp gr 0.90)–water, 6:3:1 (v/v); D, ethanol–water, 7:3 (v/v); E, ethyl acetate–1-propanol–water, 4:1:2 (v/v) upper phase. [d] See ref 22. [e] See ref 10.

Baker Chemical Co. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

The trimethylsilyl derivative of 5(4)-(3,3-dimethyl-1-triazeno)imidazole-4(5)-carboxamide (DIC)[24] was prepared using the general procedure of Wittenburg.[25] DIC was added to an excess of hexamethyldisilazane containing a catalytic quantity (10 mg) of ammonium sulfate and the reaction mixture heated at reflux temperature (130°) under anhydrous conditions for 7 hr. During this period a clear solution was effected and the reaction was protected from light. The excess hexamethyldisilazane was then removed under reduced pressure and the oily residue was used in the condensation procedure without further purification.

1-(2,3,5-Tri-*O*-acetyl-β-ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (3) and 1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4-(3,3-dimethyl-1-triazeno)imidazole-5-carboxamide (4).—A solution of 2,3,5-Tri-*O*-acetyl-D-ribofuranosyl bromide,[26] prepared from 9.5 g (29.8 mmol) of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, in dry acetonitrile (40 ml) was added to the trimethylsilyl derivative of DIC prepared from 5.0 g (27.4 mmol) of DIC. The reaction mixture was then stirred at room temperature in a sealed vessel in the dark for 4 days. To this solution was added methanol (15 ml), water (10 ml), and a slight excess of sodium bicarbonate. The mixture was warmed gently on a steam bath for 15 min and then evaporated to dryness under reduced pressure (water bath 40°). The remaining traces of water were removed by coevaporation with absolute ethanol and the residual syrup was extracted with chloroform (three 100-ml portions). The chloroform extract was washed with cold water (three 100-ml portions) and the chloroform phase was dried over anhydrous magnesium sulfate. The chloroform layer was evaporated *in vacuo* to provide a light tan syrup. This syrup was dissolved in ethanol (30 ml) and then allowed to stand at 4° for 12 hr. The crystalline solid (2.49 g) which had separated from solution was collected by filtration and washed with a small amount (10 ml) of cold ethanol. An additional quantity (0.68 g) of **4** was obtained when the above procedure was repeated. The ethanol filtrates were evaporated to a syrup, dissolved in a minimal amount of chloroform, and applied to a silica gel column (2.2 × 70 cm). The column was eluted with chloroform (300 ml) and chloroform–methanol (49:1, v/v, 1.5 l.), with 100-ml fractions being collected. Fractions 6–8 were combined and evaporated to yield 0.71 g of **4** (32.2%). Fractions 10–15 were pooled and evaporated to provide **3** (2.1 g, 17.4%) as a hard foam (homogeneous on tlc). Total yield of nucleoside material was 49.6%.

Recrystallization of **4** from ethanol provided an analytical sample: mp 159–160°; $[\alpha]^{27}D$ −39.2° (*c* 0.98, EtOH); uv λ_{max}^{MeOH} 322 nm (ε 18,277), 237 (12,992); uv λ_{min}^{MeOH} 256 nm (ε 5373); pmr (DMSO-d_6) δ 8.05 (s, 1, 2 H), 7.61 (vbd,[27] 2, $CONH_2$), 3.38 (vbd, 6, NCH_3), 6.80 (d, 1, $J_{1',2'}$ = 4 Hz, 1′ H), 2.11 (s, 9, $COCH_3$).

Anal. Calcd for $C_{17}H_{24}N_6O_8$: C, 46.36; H, 5.49; N, 19.08. Found: C, 46.41; H, 5.44; N, 18.85.

1-(β-D-Ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (5).—A solution of **3** (2.1 g, 4.76 mmol) in methanol (50 ml, previously saturated at −5° with ammonia) was allowed to stand at room temperature for 4 days in a sealed pressure bottle. The solvent was then removed *in vacuo*, and the residual solid was dissolved in methanol (20 ml) and allowed to stand at room temperature for 12 hr. The crystalline solid which had precipitated was collected by filtration to provide 1.13 g (75.5%) of **5**. An analytical sample was prepared by recrystallization from methanol: mp 215–217°; $[\alpha]^{27}D$ −290.6° (*c* 0.5, H_2O); uv $\lambda_{max}^{pH\ 1}$ 324 nm (ε 16,186), sh 270 (7543), 223 (11,943); $\lambda_{min}^{pH\ 1}$ 249.5 nm (ε 6097); $\lambda_{max}^{pH\ 11}$ 333 nm (ε 13,389), 236.5 (17,537); $\lambda_{min}^{pH\ 11}$ 273 nm (ε 6254); λ_{max}^{MeOH} 336 nm (ε 14,143), 235.5 (15,275); λ_{min}^{MeOH} 267 nm (ε 4777); pmr (DMSO-d_6) δ 7.67 (s, 1, 2 H), 7.00 (vbd, 2, $CONH_2$), 3.35 (vbs, 6, NCH_3), 6.03 (d, 1, $J_{1',2'}$ = 4 Hz, 1′ H).

Anal. Calcd for $C_{11}H_{18}N_6O_5$: C, 42.08; H, 5.78; N, 26.76. Found: C, 42.03; H, 5.73; N, 26.62.

5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (7).—1-(β-D-Ribofuranosyl)-5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (**5**) (0.295 g, 0.93 mmol) was dissolved in 50 ml of water. Raney nickel[28] (1.2 g, wet weight) was added to this solution followed by 5 drops of ammonium hydroxide (sp gr 0.90) and the mixture hydrogenated, with shaking, in a Paar hydrogenator at 40 psi for 6 hr. The catalyst was removed by filtration and washed with water (three 25-ml portions), and the filtrate and washings were combined and evaporated *in vacuo* to afford a pink glass. The glass was dissolved in a small amount of boiling ethanol (15 ml) and allowed to stand at room temperature for 12 hr to yield clusters of pink rosettes (0.195 g, 81%): mp 215–216°[29] (lit.[3] 213–214°); $[\alpha]^{27}D$ −62.4° (*c* 0.495, H_2O) [lit.[6] $[\alpha]^{26}D$ −63.0° (*c* 1.0, H_2O)]; uv, ir, and chromatographic mobilities were identical with those of an authentic sample.[22]

1-(β-D-Ribofuranosyl)-4-(3,3-dimethyl-1-triazeno)imidazole-5-carboxamide (6).—A solution of **4** (2.23 g, 5.06 mmol) in methanol (60 ml, previously saturated at −5° with ammonia) was allowed to stand at room temperature for 4 days in a sealed pressure bottle. The crystalline white solid (1.51 g, 94.6%) which had precipitated was collected by filtration and washed with a small amount of methanol. Recrystallization of the product from water provided an analytical sample as needles: mp (softens at 125° and resolidifies) 218–220°; $[\alpha]^{27}D$ +9.0° (*c* 0.5, H_2O); uv $\lambda_{max}^{pH\ 1}$ 322 nm (ε 21,687), sh 270 (8077); $\lambda_{min}^{pH\ 1}$ 247 (ε 4652); $\lambda_{max}^{pH\ 11}$ 326 nm (ε 18,669), 239 (11,315); $\lambda_{min}^{pH\ 11}$ 258 nm (ε 4872) λ_{max}^{MeOH} 324 nm (ε 18,229), 238.5 (12,949); λ_{min}^{MeOH} 259 nm (ε 5343), pmr (DMSO-d_6) δ 8.18 (s, 1, 2 H), 7.53 (vbd, 2, $CONH_2$), 3.36 (vbd, 6, NCH_3), 6.56 (d, 1, $J_{1',2'}$ = 2 Hz, 1′ H).

Anal. Calcd for $C_{11}H_{18}N_6O_5 \cdot {}^1/_2H_2O$: C, 40.86; H, 5.92; N, 26.00. Found: C, 40.78; H, 6.14; N, 26.03.

4-Amino-1-(β-D-ribofuranosyl)imidazole-5-carboxamide (8).—1-(β-D-Ribofuranosyl)-4-(3,3-dimethyl-1-triazeno)imidazole-5-carboxamide (**6**) (0.200 g, 0.64 mmol) was dissolved in 50 ml of water. Raney nickel[28] (0.80 g, wet weight) was added to this solution followed by 4 drops of ammonium hydroxide (sp gr 0.90) and the mixture hydrogenated, with shaking, in a Paar hydrogenator at 40 psi for 6 hr. The catalyst was removed by filtration and washed with water (three 25-ml portions), and the filtrate and washings were then combined and evaporated *in vacuo* to afford a colorless powder. The powder was dissolved in methanol (10 ml) and allowed to stand at 5° for 18 hr to yield white crystals (0.118 g, 71%): mp 187–189°[29] (lit.[7] 187–189°); $[\alpha]^{27}D$ −29.9 (*c* 0.975, H_2O) [lit.[10] $[\alpha]^{26}D$ −30.9° (*c* 1.0, H_2O)]; uv, ir, and chromatographic mobilities were found to be identical with those of an authentic sample.[10]

Registry No.—**4**, 28405-60-9; **5**, 28405-61-0; **6**, 28455-56-3; **7**, 2627-69-2; **8**, 7132-71-0.

(24) The authors wish to thank Dr. Robert E. Engle, Cancer Chemotherapy National Service Center, National Cancer Institute, for the generous gift of 5(3)-(3,3-dimethyl-1-triazeno)imidazole-4(5)-carboxamide (DIC) and Dr. R. A. Long for helpful suggestions on the synthesis of **7** and **8**.

(25) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964).

(26) H. Zimmer, A. Koine, and H. Nimz, *Chem. Ber.*, **93**, 2705 (1960).

(27) vbd = very broad doublet; vbs = very broad singlet; s = singlet.

(28) Purchased from W. R. Grace and Co., South Pittsburgh, Tenn.

(29) No change on taking mixture melting point with authentic sample.

Evidence for the Structures of Steroidal *N*-Phenyl[3,2-*c*]pyrazoles. Attempted Dehydrogenation to Indazoles

LELAND J. CHINN

Division of Chemical Research, G. D. Searle & Co., Chicago, Illinois 60680

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19-Nor-1′-phenyl-4,17(20)-pregnadieno[3,2-*c*]pyrazole (**4**) and 19-nor-2′-phenyl-2,4,17(20)-pregnatrieno[3,2-*c*]pyrazole (**5**) were dehydrogenated with dichlorodicyanobenzoquinone to afford 19-nor-1′-phenyl-4,6,17(20)-pregnatrieno[3,2-*c*]pyrazole (**10**) and 19-nor-2′-phenyl-1(10)-2,4,17(20)-pregnatetraeno[3,2-*c*]pyrazole (**9**), respectively. The ultraviolet spectrum of **9** resembles very much that of 3-methyl-1-phenylindazole (**6**) and is definitely different from that of 2-phenylindazole (**7**) so that the correctness of the structural assignments is confirmed.

Steroids with a pyrazole ring fused to ring A have been reported to possess unusually high biological activities.[1,2] In general, they are prepared by condensing a 3-keto steroid at the 2 position with an ester. The resultant β-dicarbonyl compound is then reacted with a monosubstituted hydrazine. Two isomeric pyrazoles, 1′-substituted steroidal [3,2-*c*]pyrazole (**1**), and 2′-substituted steroidal [3,2-*c*]pyrazole (**2**), are obtained. The two pyrazoles show distinctive spectral characteristics.

Thus, of the two pyrazoles, **1** and **2** (Δ^4, R = C_6H_6, R′ = H, R^2 = CH_3), one absorbs maximally at ~300 mμ (ε ~32,000) while the other shows maximal absorption at ~260 mμ (ε ~17,000).[2] Hirschmann, *et al.*,[2] proposed that the pyrazole which absorbs at 300 mμ has structure **1** while that absorbing at 260 mμ has structure **2**. On the basis of the difference in ultraviolet absorption of the two pyrazoles and on the basis of the similarity in the nmr splitting pattern of the phenyl protons of aniline to the phenyl protons of the pyrazole which absorbs maximally at the greater wavelength, they concluded that the pyrazole which absorbs at 260 mμ exhibits steric inhibition of resonance. Therefore, its structure must be **2**, for in **2** there is steric interaction between the ortho hydrogen of the phenyl ring and the C-4 hydrogen of the steroid nucleus.[3] The mechanism by which the pyrazole ring is formed was advanced as additional evidence in support of this conclusion.

Although the interpretation of Hirschmann, *et al.*, is not unreasonable, there is, nevertheless, a need for more conclusive evidence.

Recent publications on the preparation of 1-aryl- and 2-arylindazoles from aromatic ketones and aldehydes[4] suggested to us the possibility of providing independent support for the structures of the *N*-aryl steroidal pyrazoles by comparing the ultraviolet spectra of the indazoles derived from the dehydrogenation of steroidal *N*-aryl-19-nor[3,2-*c*]pyrazoles with the spectra of appropriate 1-aryl- and 2-arylindazoles prepared from the aromatic carbonyl compounds.

This report describes the preparation and dehydrogenation of the two isomeric steroidal *N*-phenylpyrazoles, **4** and **5**, obtained from 19-norpregna-4,17(20)-dien-3-one (**3**)[5] and the comparison of the spectra of their dehydrogenated products with the spectra of 3-methyl-1-phenylindazole (**6**)[4a,6] [λ_{max} 251 mμ (ε 34,050), 304–307 (13,500)] and 2-phenylindazole (**7**)[4a,b] [λ_{max} 235–236 mμ (ε 21,700), 294–295 (15,800)].

19-Nor-1′-phenyl-4,17(20)-pregnadieno[3,2-*c*]pyrazole (**4**) and 19-nor-2′-phenyl-2,4,27(20)-pregnatrieno[3,2-*c*]-pyrazole (**5**) were synthesized from **3** by the method described by Hirschmann, *et al.*[2] One of the pyrazoles absorbs at 297–298 mμ (ε 28,000) while the other absorbs at 259–261 mμ (ε 16,750). The phenyl protons of the pyrazole which absorb at 297–298 mμ appear as a complex multiplet between 429 to 463.5 cps (downfield with respect to internal tetramethylsilane at 60 Mc in deuteriochloroform) in the nmr spectrum while the same protons of the isomeric pyrazole appear as a single peak at 446 cps. In addition, the vinyl proton at C-4 of the pyrazole absorbing at 297–298 mμ resonates at 382 cps while that of the pyrazole absorbing at 259–261 mμ resonates at 373 cps. In accordance with the interpretation of Hirschmann, *et al.*,[2] the pyrazole absorbing at 297–298 mμ is assigned structure **4** and that absorbing at 259–261 mμ is assigned structure **5**. In **4**, the phenyl ring is in the plane of the pyrazole ring so that the ortho protons of the phenyl ring are more deshielded than the meta and para protons. This gives rise to the multiplet that is observed in the region of 429–463.5 cps. In contrast, the phenyl ring of **5** is out of the plane of the pyrazole ring because of steric repulsion. The time-averaged magnetic field effect on the phenyl protons due to the pyrazole ring is such that these protons appear to be equivalent.[7] Since the phenyl ring of **5** is not coplanar with the pyrazole ring, the C-4 proton of **5** is more apt to be shielded than the corresponding proton of **4**. Consequently, the C-4 proton of **5** would be expected to resonate at a higher field than that of **4**. Experimentally, this is, indeed, what is observed.

Dehydrogenation of **4** and **5** was achieved with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in acetone. We had expected that the elimination of 1 mol equiv of hydrogen from **4** and **5** would give the indazoles, 19-nor-1′-phenyl-1(10),4,17(20)-pregnatrieno[3,2-*c*]pyrazole (**8**) and 19-nor-2′-phenyl-1(10)-2,4,17(20)-pregnatetraeno-

(1) (a) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Amer. Chem. Soc.*, **83**, 1478 (1961); (b) R. O. Clinton, R. L. Clarke, F. W. Stonner, A. J. Manson, and K. F. Jennings, *J. Org. Chem.*, **27**, 2800 (1962).

(2) R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H. Fried, R. Ellis, G. J. Kent, and M. Tishler, *J. Amer. Chem. Soc.*, **86**, 1520 (1964).

(3) *Cf.* S. Tabak, I. I. Grandberg, and A. N. Kost, *Tetrahedron*, **22**, 2703 (1966).

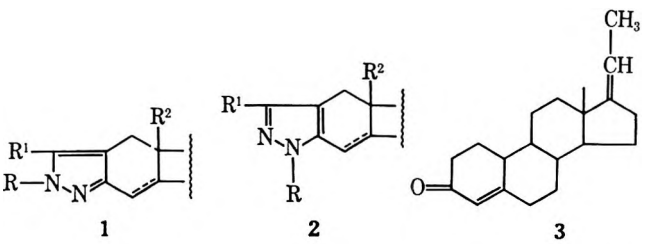
(4) (a) W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.*, 3048 (1965); (b) L. Kobechek and H. Takimoto, *J. Org. Chem.*, **29**, 1150 (1964); (c) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, 4831 (1965).

(5) F. B. Colton, L. Nysted, B. Riegel, and A. L Raymond, *J. Amer. Chem. Soc.*, **79**, 1123 (1957).

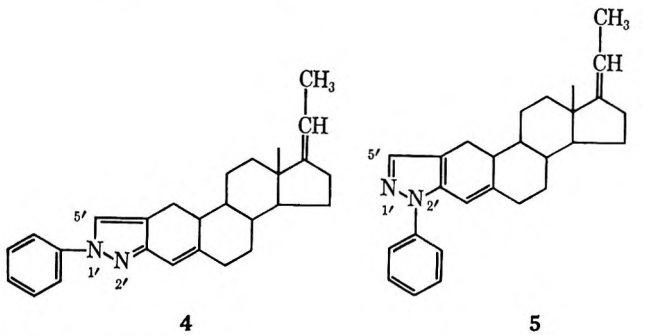
(6) Kindly supplied by Professor R. O. C. Norman, to whom we are indebted.

(7) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

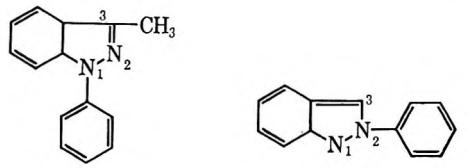
[3,2-*c*]pyrazole (**9**), respectively. Because one of the indazoles has an *o*-quinoid structure while the other has a benzenoid structure, the two indazoles were expected to be distinguishable by spectroscopic means.[8]



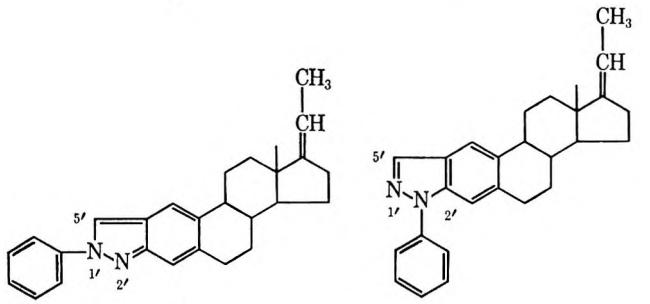
1 **2** **3**



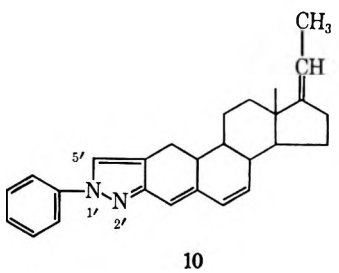
4 **5**



6 **7**



8 **9**



10

Instead of **8**, the dehydrogenated product obtained from **4** proved to be 19-nor-1′-phenyl-4,6,17(20)-pregnatrieno[3,2-*c*]pyrazole (**10**). Besides the protons at C-5′ and -20, its nmr spectrum reveals the presence of three additional vinyl protons. These protons appear as a singlet at 385 cps and a pair of doublets centered at 351 and 375 cps. Each of the doublets exhibits a spin–spin coupling constant of 10 cps. The singlet is assigned to the C-4 proton and the pair of doublets are assigned to the protons at C-6 and -7. The extremely high levorotation, which this product displays, is a further indication that the newly introduced double bond is located at the 6,7 position.[1a] The ultraviolet spectrum of **10** shows maximal absorption at 246.5–248.5 mμ (ε 9030) and 320–321 (37,700), and it is clearly different from the spectrum of 3-methyl-1-phenylindazole (**6**) and that of 2-phenylindazole (**7**).

Dehydrogenation of **5** gives the expected product **9**. Its nmr spectrum shows no vinyl protons other than those at C-5′ and -20. The ultraviolet spectrum of **9** shows maximal absorption at 256.5 mμ (ε 28,450) and 306 (7900). This spectrum resembles greatly that of 3-methyl-1-phenylindazole (**6**), and it differs distinctly from that of 2-phenylindazole (**7**).

These results indicate that the structures of the two isomeric pyrazoles obtained from **3** are correctly formulated. Hence, Hirschmann, *et al.*, were correct in their conclusion.[2] However, in view of the study of Tensmeyer and Ainsworth,[7] the inference which the former drew[2] from a comparison of the nmr splitting pattern of the phenyl protons of the pyrazoles with that of the phenyl protons of aniline is worth noting. In aniline, the ortho protons are shifted upfield by resonance while, in an unhindered phenylpyrazole, the same protons are shifted downfield because of the deshielding effect of the pyrazole ring.[7] Consequently, the similarity that they observed[2] in the phenyl proton region of the nmr spectra between aniline and the steroidal 1′-phenyl[3,2-*c*]pyrazole must be attributed to an interaction of the nitrogen atom with the aromatic protons, an interaction which is diminished in the 2′-phenylpyrazole as a result of the lack of coplanarity.

Experimental Section[9]

2-(Hydroxymethylene)-19-norpregna-4,17(20)-dien-3-one.—To a mixture of 2.5 g of 19-norpregna-4,17(20)-dien-3-one,[5] 10 ml of dry benzene and 2 ml of ethyl formate, stirred in an ice bath, was added 1.2 g of a 56% dispersion of sodium hydride in mineral oil. The reaction mixture was stirred in the ice bath for 2.5 hr, the ice being allowed to melt. The resultant brown paste was carefully diluted with water and then with benzene. The benzene phase was separated and extracted successively with water and 5% sodium hydroxide. The combined aqueous, alkaline phases were acidified by addition to a mixture of ice and 5% hydrochloric acid. The mixture was extracted with methylene chloride. The methylene chloride extract was dried (Na_2SO_4) and distilled to dryness to afford the product as a viscous yellow-brown oil, which imparted a purple-brown color to an alcoholic solution of ferric chloride.

19-Nor-1′-phenyl-4,17(20)-pregnadieno[3,2-*c*]pyrazole (4) and 19-Nor-2′-phenyl-2,4,17(20)-pregnatrieno[3,2-*c*]pyrazole (5).—The aforementioned crude hydroxymethylene compound was dissolved in 30 ml of 95% ethanol. After 1 ml of phenylhydrazine was added, the reaction mixture was heated under reflux in a nitrogen atmosphere for 1 hr. Then the reaction mixture was distilled to dryness under reduced pressure. The residue was dissolved in methylene chloride. The methylene chloride solution was washed with water, dried (Na_2SO_4), and distilled to dryness to afford a brown tarry product.

The tar was chromatographed on 300 g of neutral alumina. Elution of the column with 20% hexane in benzene gave in succession 0.41 g of **4** and 1.06 g of **5**. Crystallization of **4** from ether–hexane gave 0.25 g of a colorless crystalline product, mp 138–141.5°. Another crystallization from ether–hexane raised the mp to 141.5–143.5°; $[\alpha]^{26}D$ −34°; (*c* 1, $CHCl_3$); λ_{max}^{MeOH} 297–298 mμ (ε 28,000); λ_{min} 253–255 mμ (ε 5120); λ_{max}^{KBr} 3.28,

(8) *Cf.* V. Rosseau and H. G. Lindwell, *J. Amer. Chem. Soc.*, **72**, 3047 (1950); J. Elguero, A. Fruchlier, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 2075 (1966).

(9) Melting points were taken on a Fisher-Johns melting block and are corrected. The nmr spectra were determined in deuteriochloroform on a Varian A-60 instrument with tetramethylsilane as an internal standard.

6.12, 6.25, 6.35 μ; nmr 429–463.5 (m), 382 (s), 304 (q, J = 6.5 cps), 93 (d, J = 6.5 cps), 48 cps (s).

Anal. Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.29. Found: C, 84.60; H, 8.30; N, 7.68.

Crystallization of **5** from ether–hexane gave 0.66 g of a yellow crystalline product: mp 156–160°; $[\alpha]^{26}D$ +26° (*c* 1, $CHCl_3$); λ_{max}^{MeOH} 259–261 mμ (ε 16,750); λ_{min} 234.5–235.5 mμ (ε 8725); λ_{max}^{KBr} 3.25, 6.15, 6.22 μ; nmr 446 (s), 442 (s), 373 (s), 303 (q, J = 7 cps), 93 (d, J = 7 cps), 45 cps (s).

Anal. Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.29. Found: C, 84.52; H, 8.30; N, 7.32.

19-Nor-2′-phenyl-1(10)-2,4,17(20)-pregnatetraeno[3,2-*c*]pyrazole (9).—To a warm solution of 0.48 g of 19-nor-2′-phenyl-2,4,17(20)-pregnatrieno[3,2-*c*]pyrazole (**5**) in 40 ml of acetone was added portionwise with stirring over a period of 1 hr 0.35 g of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. The reaction mixture, which contained a crystalline product, was allowed to stand at room temperature for an additional hour. Then the colorless, crystalline product was collected, washed with acetone, and dried, yield 0.27 g, mp 198.5–200.5°. The combined filtrate and washings were concentrated to 25 ml. On standing at room temperature for 15 hr, the resultant mixture afforded an additional 0.04 g of **9**, mp 196.5–201.5°. Crystallization of the first crop from acetone raised the mp to 201.5–204.5°; $[\alpha]^{26}D$ +15° (*c* 1, $CHCl_3$); $\lambda_{max}^{CHCl_3-MeOH}$ 256.6 mμ (ε 28,450), 306 (7900); λ_{min} 232.5–233.5 mμ (ε 8860), 283.5–286 (5175); λ_{max}^{KBr} 3.27, 6.12, 6.13 μ; nmr 485.5 (s), 442.5–461 (m), 307 (q, J = 7 cps), 180 (t, J = 5 cps), 95 (d, J = 6.5 cps), 47.5 cps (s).

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.70; H, 7.82; N, 7.61.

19-Nor-1′-phenyl-4,6,17(20)-pregnatrieno[3,2-*c*]pyrazole (10).—To a warm solution of 1.01 g of 19-nor-1′-phenyl-4,17(20)-pregnadieno[3,2-*c*]pyrazole (**4**) in 30 ml of acetone was added portionwise with stirring over a period of 1 hr 0.78 g of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. The reaction mixture was allowed to stand at room temperature for 16 hr and then treated with a dilute solution of sodium sulfite. The reaction mixture was concentrated. The residue was diluted with ice water. The resultant brown solid was collected, washed with water, and dried. It was chromatographed on 100 g of neutral alumina. Elution of the column with 30% hexane in benzene gave 0.33 g of a pale yellow crystalline product, mp 183–186°. Crystallization from acetone gave **10** as colorless crystals, mp 187.5–190°. Admixed with **9**, it melted at 168–177°; $[\alpha]^{26}D$ −514° (*c* 0.25, $CHCl_3$); $\lambda_{max}^{CHCl_3-MeOH}$ 246.5–248.5 mμ (ε 9030), 320–321 (37,700); λ_{min} 237.5–239 mμ (ε 8500), 271–273 (5550); λ_{max}^{KBr} 3.28, 6.24, 6.38 μ; nmr 435.5–453.5 (m), 377 (d, J = 10 cps), 351 (d, J = 10 cps), 303.5 (*q*, J = 65 cps), 184 (d, J = 7 cps), 93 (d, J = 6.5 cps), 47.5 cps (s).

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 85.03; H, 7.99; N, 7.45.

Ultraviolet Absorption Maxima and Minima of 3-Methyl-1-phenylindazole (6):[4a,5] λ_{max}^{MeOH} 251 mμ (ε 34,050), 304–307 (13,500); λ_{min} 229–231 mμ (ε 8400), 278 (5080).

Ultraviolet Absorption Maxima and Minima of 2-Phenylindazole (7).—This substance was prepared according to the procedure of Krbechek and Takimoto;[4b] λ_{max}^{MeOH} 235–236 mμ (ε 21,700), 294–295 (15,800), λ_{min} 257 mμ (ε 2290).

Registry No.—**4**, 28504-58-7; **5**, 28504-59-8; **6**, 1575-29-7; **7**, 3682-71-1; **9**, 28504-62-3; **10**, 28504-63-4.

Synthesis of 1,10,11,11a-Tetrahydro-11a-methyl-2*H*-naphth[1,2-*g*]indol-7-ol, an Equilenin-Like 15-Aza Steroid[1]

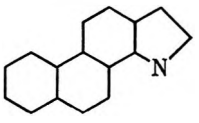
JOHN G. MORGAN,[2a] K. DARRELL BERLIN,* NORMAN N. DURHAM,[2b] AND ROBERT W. CHESNUT[2b]

Departments of Chemistry and Microbiology, Oklahoma State University, Stillwater, Oklahoma 74074

Received November 23, 1970

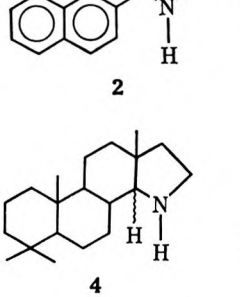
This study reports the synthesis and characterization of the 15-azaequilenin derivative 1,10,11,11a-tetrahydro-11a-methyl-2*H*-naphth[1,2-*g*]indol-7-ol (**6a**) as well as the methyl ether **6b** of the above compound and the novel model compound 3,3a,4,5-tetrahydro-3a-methyl-2*H*-benz[*g*]indole (**7**).

Steroids which have nitrogen incorporated in the cyclopentaphenanthrene nucleus have been shown to possess a wide range of physiological activities.[3–5] Interestingly, naph[1,2-*g*]indoles or 15-aza steroids of general formula **1** represent an almost totally neglected area of organic synthesis despite the fact that these compounds combine the steroid and indole nuclei in a single structure and may be expected to demonstrate significant biological activity.



1

A literature search revealed only four examples of 15-monoaza steroid structures. Naphthisatin **2** was synthesized in the 1930's as a "synthetic decarboxylase,"[6] and compounds **3–5** were intermediates in steroid–terpene structure correlations.[7] No pharmacological data on the aforementioned compounds are available.



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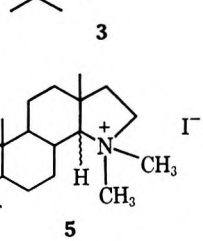

3

4

5

(1) We gratefully acknowledge support of this work by a grant to the Oklahoma State University from the American Cancer Society, Grant IN-91A. Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971. We thank the Merck Sharp and Dohme Co. for partial support.

(2) (a) Department of Chemistry; NDEA Fellow, 1966–1969; this work is abstracted in part from the thesis submitted in partial fulfillment of the Doctor of Philosophy degree in the Oklahoma State University. (b) Department of Microbiology.

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(4) M. Martin-Smith and F. Sugrue, *ibid.*, **16**, 568 (1964).

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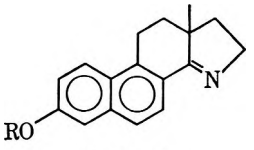
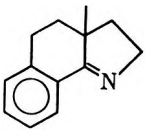
(6) W. Langenbeck and K. Weissenborn, *Ber.*, **72** (B), 724 (1939).

(7) M. Fetizon and M. Golfier, *Bull. Soc. Chim. Fr.*, 870 (1966).

This study reports the complete synthesis and characterization of the 15-azaequilenin derivative, 1,10,11,-11a-tetrahydro-11a-methyl-2*H*-naphth[1,2-*g*]indol-7-ol (**6a**), as well as the unique benzindole **7** produced in model-system studies.

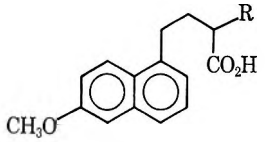


6a, R = H
b, R = OCH_3

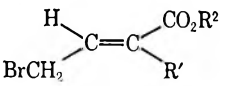


7

The synthesis of **6a** requires the naphthalenebutyric acid **8a**, previously prepared by a variety of laborious multistep processes.[8-10] In this study the general



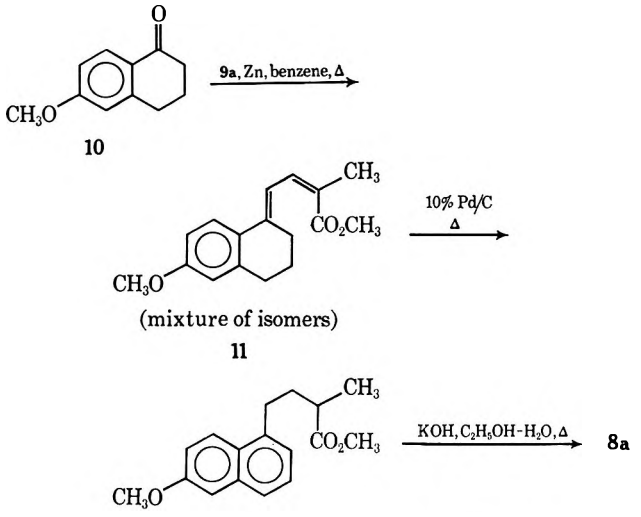
8a, R = CH_3
b, R = H



9a, R′ = R² = CH_3
b, R′ = H; R² = C_2H_5

method of Stork[11] was applied to the synthesis of **8a** but using the bromotiglate **9a** rather than the bromocrotonate **9b** employed by Stork (Scheme I). Actually,

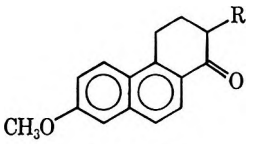
SCHEME I



the diene ester **11** was distilled but it undoubtedly was a mixture of isomers.

The bromo ester **9a**, prepared by the method of Inhoffen and coworkers,[12] could only be isolated in a crude state (see Experimental Section). Crude **9a**, however, proved satisfactory for use in the synthesis of **8a**.

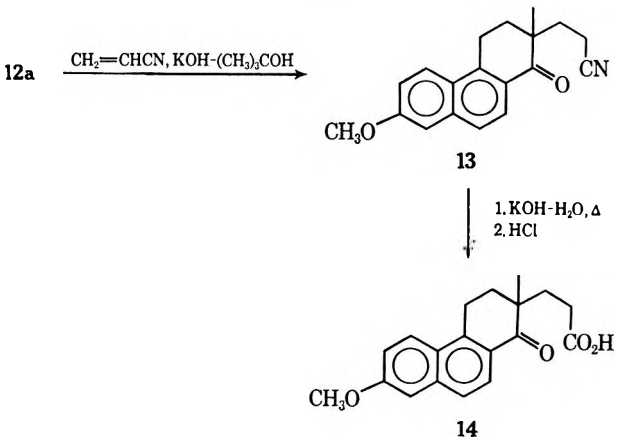
Acid **8a** was then cyclized with polyphosphoric acid[13] to yield the known phenanthrone **12a**.[8-10] This cyclization, which can be performed in 30 min in an open beaker, produces **12a** in 86% yield and is thus superior in terms of ease and convenience to any published method for the conversion of **8a** to **12a**. Ketone **12a**



12a, R = CH_3
b, R = H

was condensed with acrylonitrile in *tert*-butyl alcohol in the presence of aqueous KOH (this general method is recorded[14,15]). The resulting nitrile, **13** (not isolated), upon hydrolysis provided the novel and previously unknown phenanthrenepropionic acid **14** (Scheme II) in a yield of 56.5% (based on **12a**). This

SCHEME II



yield was determined from the weighed compound obtained after one chromatogram and two recrystallizations.

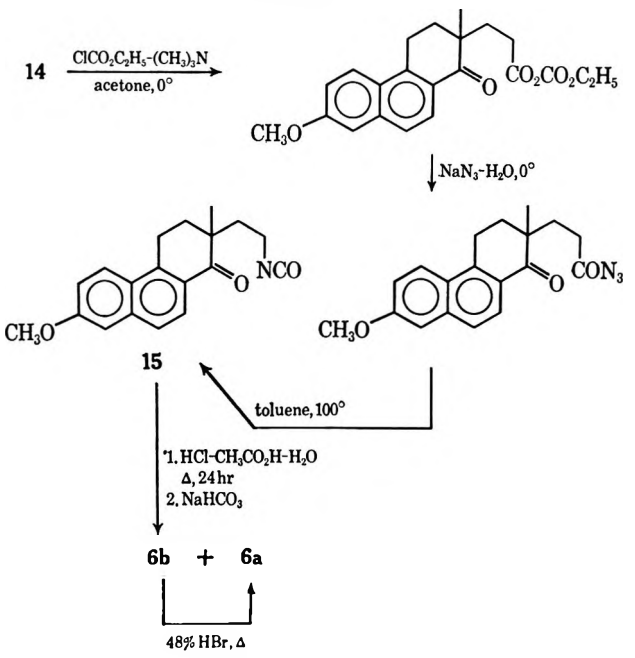
Acid **14** was subjected to the modified Curtius rearrangement procedure of Weinstock[16] as adapted by Fetizon and Golfier.[7] The resulting steroidal imine ether **6b** was then hydrolyzed with boiling 48% HBr to the title compound **6a**. Some **6a** was, in fact, produced directly during the hydrolysis of isocyanate **15**, especially if prolonged heating was employed (Scheme III).

The α-methylation of 1-tetralone was examined as a model system for the preparation of **12a** from the unsubstituted phenanthrone **12b** (compound **12b** being conveniently available from **8b**).[11] 2-Methyl-1-tetralone (**16**) was successfully produced in high yield from 1-tetralone by application of the methods of Ireland and Marshall,[17] *i.e.*, reductive desulfurization of the 2-*n*-butylthiomethylene derivative of a ketone. Unfortunately, **12a** could not be realized in satisfactory condition by the foregoing approach, since a complicated mixture was obtained in the reduction step.

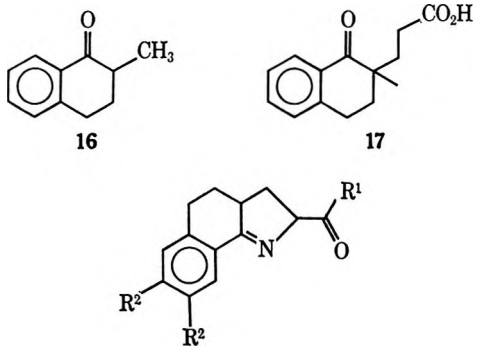
Compound **16** was subjected, in a pilot study, to the same series of reactions eventually used with phenanthrone **12a**. The synthesis of the resulting novel 3,3a,4,5-tetrahydro-3a-methyl-2*H*-benz[*g*]indole (**7**)

(8) W. Bachmann, S. Kushner, and A. Stevenson, *J. Amer. Chem. Soc.*, **64**, 979 (1942).
(9) G. Haberland and E. Blanke, *Ber.*, **70**, 169 (1937).
(10) A. Wilds and W. Close, *J. Amer. Chem. Soc.*, **69**, 3079 (1947).
(11) G. Stork, *ibid.*, **69**, 2936 (1947).
(12) H. Inhoffen, S. Bork, and U. Schweiter, *Justus Liebigs Ann. Chem.*, **880**, 1 (1953).
(13) F. Snyder and F. Werber, "Organic Syntheses," Collect. Vol. III, E. Horning, Ed., Wiley, New York, N. Y., 1963, p 798.
(14) R. Frank and F. Pierle, *J. Amer. Chem. Soc.*, **73**, 724 (1951).
(15) M. Robinson, *Tetrahedron*, **1**, 49 (1957).
(16) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).
(17) R. Ireland and J. Marshall, *ibid.*, **27**, 1616 (1962).

SCHEME III



represents only the second time that the production of this type of compound has been recorded. Several members of the general formula **18** were reported to be "adrenolytic central nervous system depressants and analgetic agents."[18] The hydrochloride of **18** (R^1 = OH; R^2 = H) has been prepared by the acid hydrolysis of the condensation product of *N,N,N*-trimethyl-1,2,3,4-tetrahydro-1-oxo-2-naphthalenemethylammonium chloride and diethyl acetamidosodiomalonate.[18]



Aza steroids **6a** and **6b** have been subjected to a program of testing and produced cell lysis in *Bacillus subtilis* and inhibited the growth of a species of *Flavobacterium*, *Escherichia coli*, and *Pseudomonas fluorescens*. The results of this biological survey will be reported in detail elsewhere.

Experimental Section[19]

Preparation of 6-Methoxy-α-methyl-1-naphthalenebutyric Acid (8a).[11]—A zinc strip (0.01 in. thick, 270 g, 4.1 g-atoms) was cut into approximately 0.25 by 0.5 in. pieces and washed consecutively with dilute HCl, distilled H_2O, acetone, and anhydrous ether. The zinc was then dried at 100° in an oven for about 0.5 hr before use.

The zinc, 700 ml of anhydrous, reagent-grade benzene, and 18.0 g of anhydrous $HgCl_2$ were placed in a 5-l. flask equipped with a condenser and N_2 inlet. This mixture was stirred under N_2 purge for 0.5 hr. Bromo ester **9a**[20] (260 g, 1.34 mol) and 6-methoxy-1-tetralone (**10**) [260 g, 1.48 mol (Aldrich Chemical Co.), mp 76–78° (lit.[11] mp 78.4–79°)] in 700 ml of ether and 300 ml of benzene, along with a crystal of iodine, were added at one time to the reaction flask. An exothermic reaction ensued accompanied by vigorous boiling of the solvent. At 1.5-hr intervals, 140 g (215 g-atoms) of zinc, 87 g (0.45 mol) of **9a**, and a crystal of iodine were added. This procedure was performed three times, the mixture being boiled and stirred under N_2 during the whole period.

Heating and stirring were continued for 3 hr after the last addition; the mixture was then cooled, poured into ice water, neutralized with acetic acid, and extracted with ether. The organic phase was extracted three times with 5% aqueous NH_4OH, once with H_2O, and once with saturated aqueous NaCl, and the resulting solution was dried ($MgSO_4$). After being filtered, the solution was evaporated on an aspirator and the residual oil was distilled *in vacuo*. A forerun consisting of unreacted **10** distilled at 110–150° (0.06 mm). The product amounted to 145 g (35.6% based on **10**) of crude methyl 4-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)tiglate (**11**), bp 180–200° (0.25 mm). This material is a viscous yellow oil which partially solidifies upon standing overnight.

The 145 g of **11** was heated to 250° with 23 g of 10% Pd/C for 6 hr under a CO_2 atmosphere. The mixture was then cooled, diluted with ether, filtered, and evaporated. The residue was heated at reflux for 12 hr with 50 g of KOH in 500 ml of 50:50 ethanol–H_2O. The resulting hydrolysate was diluted (H_2O), extracted three times with ether, and acidified (dilute HCl). The precipitate was filtered, washed well (H_2O), and vacuum dried to yield 120 g of dark solid. This solid was extracted with three 1.5-l. portions of boiling hexane, leaving behind a black undefined tar. On cooling, the hexane solution deposited 60 g of yellow-white crystals, mp 77–82°. Concentration of the mother liquor produced an additional 30 g of very crude **8a**. Total yield of **8a** was 90 g (24% based on **10**). An analytical sample of **8a** was crystallized from hexane: mp 85–86°, sealed tube (st) under vacuum (lit.[9] mp 86–87°); ν_{max}^{KBr} 1685 cm^{-1} (C=O); nmr (15% in $DCCl_3$) 1.26 (d, 3 H, CH_3), 1.67–3.27 (m, 5 H, CH_2 and CH), 3.82 (s, 3 H, OCH_3), 6.98–8.05 (m, 6 H, aromatic H), and 11.5 (s, 1 H, CO_2H).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.33; H, 7.07.

Preparation of 3,4-Dihydro-7-methoxy-2-methyl-1(2*H*)-phenanthrone (12a).[13]—Polyphosphoric acid (250 g of 115% PPA) was heated to 90° in a 600-ml beaker. Compound **12a** (60 g, 0.23 mol) was added and the mixture was stirred for 15 min. An additional 250 g of PPA was added and the mixture was reheated to 100° and then allowed to cool with stirring to 60°.

The resulting dark-brown syrup was poured into ice water and the yellowish solid which separated was filtered, washed well with distilled H_2O, and air-dried to yield 50.5 g of crude **12a**. This crude phenanthrone was dissolved in 350 ml of benzene, and the resulting solution was passed through 50 g (15 × 1 cm column) of alumina (Merck active aluminum oxide, neutral). The column was washed with additional benzene until no further material was eluted. Evaporation of the benzene *in vacuo* yielded 47.7 g (86%) of **12a** as a light yellow powder (mp 104.5–107.5°) suitable for use in the next step.

A 6-g sample of the above material was recrystallized three times from 50-ml portions of 1-butanol to yield an almost white, analytical sample (2.6 g) of **12a**: mp 107–108.5°, st, under vacuum (lit.[10] mp 109–110°); ν_{max}^{KBr} 1660 cm^{-1} (C=O); nmr (10% in $DCCl_3$) 1.29 (d, 3 H, CH_3), 1.56–3.44 (m, 5 H, CH_2 and CH), 3.89 (s, 3 H, OCH_3), and 7.05–8.18 (m, 5 H, aromatic H).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.83; H, 6.60.

(18) N. Gruenfeld, U. S. Patent 3,232,953 (Feb 1, 1966); *Chem. Abstr.*, **64**, 12646 (1966).

(19) Nmr spectra were obtained on a Varian A-60 unit with tetramethylsilane (TMS = 0) as internal reference. Molecular weights by mass spectral analysis were performed on an LKB-9000 prototype unit. (We thank the NSF, Grant 6B-7731, for funds given to the Biochemistry Department for the mass spectrometer.)

(20) Methyl γ-bromotiglate (**9a**) was synthesized by the method of Inhoffen and coworkers.[12] Glpc and nmr analysis of the product indicated the presence of several isomers (probably methyl γ-bromoangelate and products derived by bromination of the allylic α-methyl group). Nevertheless, this bromo ester mixture proved satisfactory for use in the above procedure.

Preparation of 1,2,3,4-Tetrahydro-7-methoxy-2-methyl-1-oxo-2-phenanthrenepropionic Acid (14).[14,15]—The phenanthrone **12a** (2.80 g, 0.0182 mol) was placed in a 250-ml round-bottom, flask (fitted with an addition funnel and a N_2 inlet) and was dissolved in 100 ml of warm (60°) *tert*-butyl alcohol containing 0.2 g of aqueous 40% KOH. The ketone was only sparingly soluble in the alcohol and the reaction mixture had to be maintained at around 60° to effect solution, even though the literature[18] recommends that the temperature be kept below 40°.

Acrylonitrile [0.62 g, 0.0182 mol (Matheson, practical, grade, bp 75–78°)], dissolved in 10 ml of *tert*-butyl alcohol, was added dropwise over a 30-min period. The reaction mixture was stirred overnight at 60° under N_2. The solvent was then removed by aspirator, and the residue was boiled 36 hr with 50 ml of aqueous 20% KOH.

The reaction mixture was then diluted (H_2O), extracted two times (ether), and neutralized (dilute HCl). The resulting precipitate was washed with H_2O and air-dried to yield 3.3 g of dark-brown solid. This material was washed through a 10 × 1 silica gel (35 g) column with hot benzene and recrystallized twice from 150 ml of benzene to yield 2.0 g (56.5%) of white, crystalline **14**: mp 157.5–159°); ν_{max}^{KBr} 1680 (acid C=O) and 1655 cm^{-1} (ketone C=O); nmr (10% in $DCCl_3$) 1.22 (s, 3 H, CH_3), 1.76–2.67 (m, 6 H, aliphatic CH_2), 3.13–3.47 (bt, 2 H, benzylic CH_2), 3.90 (s, 3 H, OCH_3), 7.00–8.20 (m, 5 H, aromatic H), and 11.41 (s, 1 H, CO_2H).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.20; H, 6.31.

The above procedure was performed successfully on ten times the above scale. When the condensation was attempted in 1,4-dioxane using Triton B as a catalyst,[21] the yield of **14** was only 49% and phenanthrone **12a** was recovered unchanged in the amount of 32%.

Preparation of 1,10,11,11a-Tetrahydro-7-methoxy-11a-methyl-2*H*-naphth[1,2-*g*]indole (6b) and 1,10,11,11a-Tetrahydro-11a-methyl-2*H*-naphth[1,2-*g*]indol-7-ol (6a).[7,16]—The phenanthrenepropionic acid **14** (23 g, 0.076 mol, mp 155–157.5°) was dissolved in 500 ml of anhydrous, reagent grade acetone in a 1-l., three-necked, round-bottom flask equipped with a thermometer, N_2 inlet, and addition funnel with $CaSO_4$ drying tube. The mixture was cooled to −5° in a salt–ice bath, and 12.2 g (0.122 mol) of triethylamine was added dropwise, the temperature being kept below 0°. Ethyl chloroformate (4.7 g, 0.122 mol, Eastman) was then added with the temperature at 0°.

The mixture was stirred in the cold for 30 min and 10.3 g (0.16 mol) of NaN_3 in 40 ml of H_2O was added dropwise, again at 0°. The mixture was stirred at 0° for 1 hr and poured into ice water.

The crystalline azide that separated amounted to 18.0 g and decomposed with partial melting at 90–100° (st, under vacuum). The azide was dissolved in 500 ml of toluene and heated on a steam bath until gas evolution ceased (1–2 hr). Toluene was removed *in vacuo;* the residue amounted to 16.0 g of the crude isocyanate **15**. Crude **15** was boiled for 24 hr with 300 ml of 1:1:1 H_2O–glacial acetic acid–concentrated HCl. The mixture was cooled, diluted (H_2O), extracted three times (ether), filtered, and then neutralized (aqueous 10% $NaHCO_3$).

The resulting yellow solid (9.0 g), which had a very broad melting range (120–220°), was warmed (50–60°) with 150 ml of benzene, and the mixture was filtered. The residue was again extracted with an additional 150 ml of benzene. The filtrates were combined and reduced to 150-ml total volume by boiling on a hot plate. Cooling the solution to room temperature caused it to deposit a small additional quantity of material. This solution was then filtered and the benzene-insoluble residues (crude **6a**) were combined and set aside.

The yellow benzene solution was passed over a 15 × 1 cm column of neutral alumina (~50 g) and the column was washed with additional benzene until no further material was eluted. The colorless benzene eluate was evaporated to dryness under aspirator vacuum. The white, amorphous residue was crystallized from acetone and then sublimed at 150° (0.04 mm) to yield 5.0 g (25% based on **14**) of **6b**: mp 180–181° (st, under vacuum); molecular weight by mass spectral analysis is 265 (calcd for $C_{18}H_{19}NO$, 265.34); ν_{max}^{KBr} 1600 cm^{-1} (C=N); nmr (10% in $DCCl_3$) 1.11 (s, 3 H, CH_3), 1.65–2.50 (m, 4 H, aliphatic CH_2), 2.94–3.47 (m, 2 H, benzylic CH_2), 3.78–4.25 (m, C=NCH_2) and 3.90 (s, OCH_3) (total 5 H), and 7.06–8.27 (m, 5 H, aromatic H).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.70; H, 7.30; N, 5.29.

The insoluble residue from the benzene extraction was dissolved in 800 ml of warm (50–60°) aqueous 2.5% NaOH. The NaOH solution was cooled and filtered to remove a very small quantity of insoluble residue. The solution was then made acid with dilute HCl, the acidified solution being held near 40° to prevent crystallization of what was apparently a sparingly soluble hydrochloride. The warm, acid solution was neutralized with aqueous 10% $NaHCO_3$, and the precipitated solid was sublimed at 250° (0.04 mm) to yield 2.5 g (13% based on **14**) of light yellow crystalline **6a**: mp 287–290°, with apparent decomposition (st, under vacuum); molecular weight by mass spectral[11] analysis is 251 (calcd for $C_{17}H_{17}NO$, 251.32); ν_{max}^{KBr} 1600 cm^{-1} (C=N); nmr (5% in C_5D_5N) 1.00 (s, 3 H, CH_3), 1.33–2.33 (m, 4 H, aliphatic CH_2), 2.96–3.46 (m, 2 H, benzylic CH_2), 3.68–4.49 (m, 2 H, C=NCH_2), 7.10–8.90 (m, 5 H, aromatic H), and 11.5–12.5 (b, 1 H, aromatic OH).

Anal. Calcd for $C_{17}H_{17}NO$: N, 5.62. Found: N, 5.76.

Compound **6b** (4.0 g, 0.015 mol) was boiled for 12 hr under N_2 with 50 ml of 48% HBr. The mixture was cooled and filtered through a glass-fritted funnel and the solid isolated was dissolved in 1 l. of warm (50°) aqueous 2% NaOH. The basic solution was filtered and neutralized with excess aqueous 10% $NaHCO_3$. The resulting solid was filtered, vacuum-dried, and sublimed [250° (0.04 mm)] to yield 2.9 g (77% based on **6b**) of **6a** identical with the material described above.

Preparation of 3,3a,4,5-Tetrahydro-3a-methyl-2*H*-benz[*g*]indole (7).—2-Hydroxymethylene-1-tetralone was prepared from 1-tetralone (Columbia) by the method of Campbell and coworkers.[22] 1-Tetralone (24.5 g, 0.168 mol) was converted to 27.3 g (92%) of the crude hydroxymethylene compound. The crude product was condensed with 1-butanethiol in the presence of *p*-toluenesulfonic acid to give a quantitative yield of crude 2-(*n*-butylthiomethylene)-1-tetralone. The crude thioether (21.6 g, 0.088 mol) was reductively desulfurized by the method of Ireland and Marshall[17] employing the deactivated Raney nickel described by Fieser and Fieser.[23]

The yield of 2-methyl-1-tetralone, bp 82–84° (0.6 mm) [lit.[1] bp 136–138° (16 mm)], was 17 g (94%), identical with authentic material by comparative glpc analysis.[24] The 2-methyl-1-tetralone (**16**) was converted in 98% yield to 1,2,3,4-tetrahydro-2-methyl-1-oxo-2-naphthalenepropionic acid (crude) by the method described earlier for the preparation of acid **14**. When phenanthrone **12a** was subjected to this procedure, glpc analysis revealed that a complex mixture had been produced.

The crude naphthalenepropionic acid (a viscous yellow oil)[25] was converted to benzindole **7** by the same method described earlier for the preparation of **6b**. Compound **7** was produced from the acid in 45% yield as a water-white liquid: bp 84–87° (0.04 mm); homogeneous by glpc analysis; ν_{max}^{neat} 1620 cm^{-1} (C=N); nmr (neat) 0.88 (s, 3 H, CH_3), 1.15–2.17 (m, 4 H, aliphatic CH_2), 2.20–3.15 (m, 2 H, benzylic CH_2), 3.50–4.20 (m, 2 H, C=NCH_2), 6.76–7.23 (m, 3 H, aromatic H), and 7.88–8.22 (m, 1 H, aromatic H with ortho keto function).

Anal. Calcd for $C_{13}H_{15}N$: N, 7.56. Found: N, 7.73.

Registry No.—**6a**, 28901-17-9; **6b**, 28901-18-0; **7**, 28901-19-0; **8a**, 28901-20-4; **11**, 28901-21-5; **12a**, 6299-09-8; **14**, 28901-23-7.

(21) H. Bruson and T. Riener, *J. Amer. Chem. Soc.*, **64**, 2851 (1942).

(22) A. Campbell, A. Schrage, and B. Campbell, *J. O-g. Chem.*, **15**, 1135 (1950).

(23) L. Fieser and M. Fieser, "Reagents of Organic Chemistry," Wiley, New York, N. Y., 1968, p 729.

(24) Appreciation is extended to Professor E. J. Eisenbraun and Dr. James M. Springer for providing the authors with an authentic sample of 2-methyl-1-tetralone.

(25) This acid was unique to this study but was not purified or fully characterized. The nmr spectrum of the acid was consistent with the proposed structure: nmr (DCCl₃) 1.18 (s, 3 H, CH_3), 1.76–2.61 (m, 6 H, aliphatic CH_2), 2.80–3.13 (bt, 2 H, benzylic CH_2), 7.02–7.61 (m, H, aromatic H), 7.87–8.11 (m, 1 H, aromatic H with ortho keto function), and 10.4 (s, 1 H, CO_2H).

Electrophilic Substitution of the Pyrido[2,1-*a*]isoindole System[1]

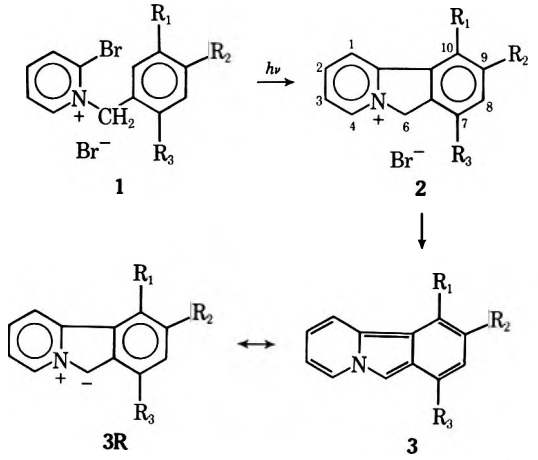
CHARLES K. BRADSHER* AND CHARLES F. VOIGT

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received October 6, 1970

Except for those substitutions which occur in strongly acid media, electrophilic substitution of the title compound **3a** occurs at position 6. The reactions exhibiting this orientation include condensation with aromatic aldehydes, benzoylation, reaction with *p*-nitrosodimethylaniline, diazonium coupling, and reaction with an activated aryl halide. There is strong evidence that nitration of **2a** occurs at position 9 and that sulfonation does not occur at position 6.

Earlier communications[2,3] have described the photochemical cyclization of 1-benzyl-2-bromopyridinium bromide (**1a**) to pyrido[2,1-*a*]isoindolium bromide (**2a**) which on treatment with sodium carbonate afforded the base **3a**. Although the nmr spectrum of the base indicates that we are dealing with an aromatic system, analogy with indolizine[4,5] suggests that one of the many possible dipolar resonance structures, the ylide **3R**, might contribute significantly to the resonance hybrid and that with suitable electrophilic reagents attack would occur at position 6.

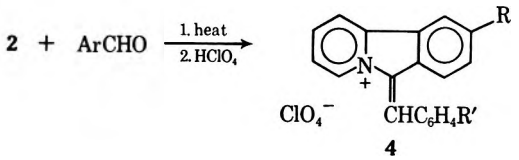


1 **2** **3R** **3**

a, $R_1 = R_2 = R_3 = H$ **d**, $R_1 = R_3 = H$; $R_2 = NO_2$
b, $R_1 = R_3 = H$; $R_2 = Br$ **e**, $R_1 = R_3 = H$; $R_2 = CN$
c, $R_1 = R_3 = Cl$; $R_2 = H$

Preliminary experiments led to the formation of intractable materials probably because of the instability of the base **3a**, and no better results were obtained by use of the somewhat more stable bases **3b** and **3c** having halogen substituted in the carbocyclic ring. Aqueous solutions of pyrido[2,1-*a*]isoindolium bromide (**2a**) are acidic (pK_a = 5.05), indicating the existence of the equilibrium 2 ⇄ 3 + HBr. This suggested that the desired electrophilic reactions might be carried out by use of the salt **2** without generating the base directly.

Refluxing the salt **2a** or its 9-bromo derivative **2b** in ethanol with aryl aldehydes led to the expected benzylidene derivatives **4** which were yellow to green in color. Nmr showed that the new products **4** had lost the two protons which had been at position 6 in the starting material, and in the case of the *p*-tolualdehyde condensation product **4b** showed that both of the possible geometrical isomers were formed. From the spectrum it would appear that 80% of the mixture had a methyl singlet at δ 2.50 and 20% had a methyl singlet at δ 2.22. It seems reasonable to assume that the isomer having the methyl group cis to the pyridinium ring would have the signal at lower field owing to the deshielding effect of the positive charge, but this is merely conjectural.

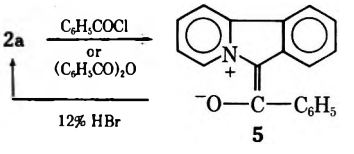


4

a, R = H; R′ = H **d**, R = Br; R′ = *p*-NO_2
b, R = H; R′ = *p*-CH_3 **e**, R = Br; R′ = *o*-Cl
c, R = Br; R′ = H

Since the arylidene condensation products **4** are in essence stilbenes, it seems possible that irradiation with ultraviolet light might lead to cyclodehydrogenation[6] or cyclodehydrohalogenation.[7] Irradiation of **4c** or **4e** for 24 hr produced no change in the uv spectrum.

Benzoylation of **2a** was readily accomplished by heating it at 100° with benzoyl chloride or benzoic anhydride. The product was not a salt but rather the betaine **5** derived from the enolate form of the 6-benzoyl derivative. The ir spectrum showed the absence of a carbonyl group and the nmr spectrum showed only aromatic protons. In deuteriochloroform there was a distinctive doublet at δ 10.56 corresponding to the proton at position 4 flanking the quaternary nitrogen, but at somewhat lower field than usually observed. If the measurement is carried out in trifluoroacetic acid, which is capable of protonating the oxygen, the doublet for the hydrogen at position 4 is found at the more normal value of δ 9.03. We regard the downfield shift when deuteriochloroform is substituted for trifluoroacetic acid as arising from the deshielding action of the negative charge on the enolate anion.



5

Like 3-acylindolizines which are readily deacylated by hot mineral acid,[8] our benzoylation product **6** was debenzoylated by heating it with 12% hydrobromic acid.

(1) This research was supported by Research Grant CA-05509 of the National Cancer Institute of the National Institutes of Health.

(2) A. Fozard and C. K. Bradsher, *Tetrahedron Lett.*, 3341 (1966).

(3) A. Fozard and C. K. Bradsher, *J. Org. Chem.*, **32**, 2966 (1967).

(4) E. T. Borrows and D. O. Holland, *Chem. Rev.*, **42**, 611 (1948).

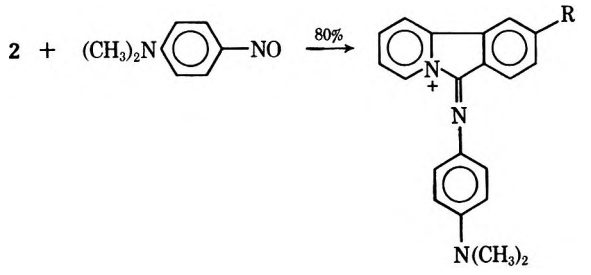
(5) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).

(6) *Cf.* F. B. Mallory, C. S. Wood, and J. T. Gordon, *J. Amer. Chem. Soc.*, **86**, 3094 (1964).

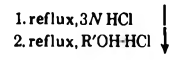
(7) S. M. Kupchan and H. C. Wormser, *J. Org. Chem.*, **30**, 3792 (1965).

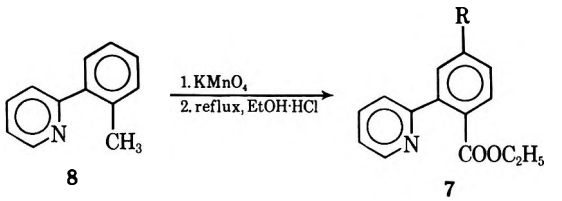
(8) *Cf.* M. Scholtz, *Ber.*, **45**, 734 (1912); A. E. Chichibabin and E. N. Stepanow, *ibid.*, **62**, 1068 (1929).

With *p*-nitroso-*N*,*N*-dimethylaniline the salt **2** was attacked at position 6, affording a dark green product **6**.



6



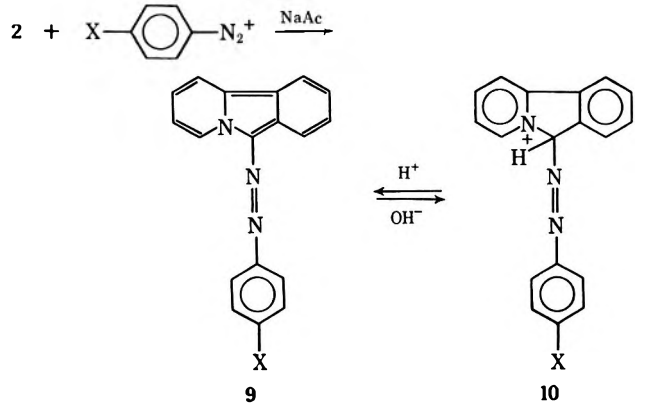


8 **7**

a, R = H
b, R = Br
c, R = NO_2

The structure of the condensation product **6** was demonstrated by hydrolysis to *o*-2-pyridylbenzoic acid which was isolated as its ethyl ester **7**. The structure of **7** was demonstrated by its synthesis from 2-*o*-tolylpyridine (**8**).

The coupling of the salt **2** or perhaps more exactly the base **3** with diazonium salts may be effected if the pH of the reaction mixture is brought to approximately 7 by addition of sodium acetate. The coupling product precipitated directly from the reaction mixture and was purified by crystallization as the hydrobromide or hydroperchlorate **10**. As can be easily seen from comparison of formulas **9** and **10**, the salts are less conjugated than the bases and understandably function as indicators.

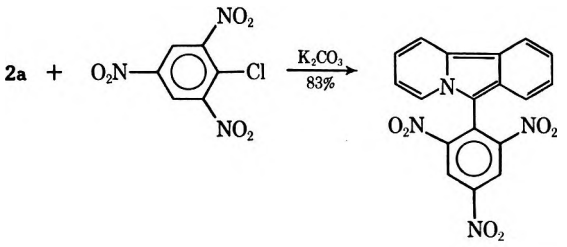


9 **10**

a, X = H
b, X = NO_2
c, X = SO_3^-

In the case of the *p*-nitro dye the color change is from yellow (**10b**) to deep purple (**9b**) and occurs at pH 5.5–6.2. The colors are very intense and easily observable below 10^{-6} *M*. The salt **10a** of the unsubstituted coupling product turned out to be very resistant to isomerization and acid hydrolysis for it was recovered unchanged after being refluxed in 12% hydrobromic acid.

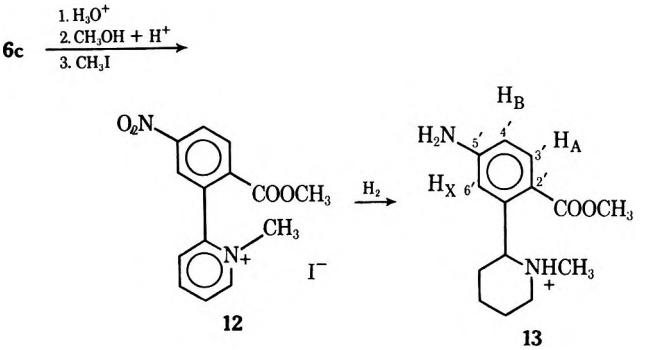
Unlike indolizine[9] our salt **2** could not be alkylated with methyl iodide or benzyl bromide. We did succeed in making what is presumably the 6-picryl derivative by using picryl chloride.



11

The electrophilic reactions of **2a** disucssed so far were carried out in a neutral or basic solution. It seemed of interest to examine two of the more classical types of electrophilic substitution of aromatic systems, nitration and sulfonation, which are usually carried out under strongly acidic conditions. Under such conditions one is probably dealing with the salt **2** and not with an equilibrium between the salt and the base (**2** ⇄ **3**). Nitration of the salt was carried out using a mixture of concentrated nitric and sulfuric acids and, as expected, the product showed a methylene peak at δ 6.25 in the nmr, indicating that the methylene group was not substituted.

It seemed likely that substitution would occur in the terminal ring more remote from the center of charge on the quaternary nitrogen and that this could be demonstrated *via* coupling of the nitration product with *p*-nitroso-*N*,*N*-dimethylaniline followed by ring opening (**6** → **7**), quaternization to form **12**, and reduction to **13**.



12 **13**

Evidence that the amino group of **13** was not at the 3′ or 6′ position was afforded by the failure to observe the typical ir absorption pattern[10] due to the out-of-plane deformation of three adjacent aromatic hydrogen atoms as well as the failure to find a complex ABC pattern in the nmr. Analysis[11] of the ABX aromatic proton pattern showed that the strongly deshielded proton (hence adjacent to the carbomethoxy group) is *strongly* coupled by a proton which must be ortho. This makes it possible to eliminate the possibility that **13** could have the amino group at the 4′ position and indicates

(9) *Cf.* M. Scholtz, *Ber.*, **45**, 1718 (1912); M. Scholtz, *Arch. Pharm. (Weinheim)*, **251**, 666 (1913).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 78.

(11) We are indebted to Professor P. W. Jeffs for this analysis.

TABLE I

6-BENZYLIDENEPYRIDO[2,1-*a*]ISOINDOLIUM SALTS (4)

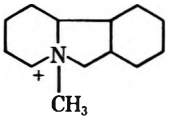
R	R′	Anion	Registry no.	Mp, °C[a]	Yield, %	Formula[b]
H	H	ClO_4	28901-40-8	196–197[c]	80[d]	$C_{19}H_{14}ClNO_4$
H	*p*-CH_3	ClO_4	28901-41-9	193–195[e]	78[d]	$C_{20}H_{16}ClNO_4$
Br	H	Br	28901-42-0	229–230[c]	90	$C_{19}H_{13}Br_2N \cdot H_2O$
Br	H	ClO_4	28901-43-1	243.5–245[c]		$C_{19}H_{13}BrClNO_4$
Br	*p*-NO_2	Br	28901-44-2	269–271[f]	72	$C_{19}H_{12}Br_2N_2O_2 \cdot H_2O$
Br	*p*-NO_2	ClO_4	28901-45-3	264–266[f]		$C_{19}H_{12}BrClN_2O_6$
Br	*o*-Cl	ClO_4	28901-46-4	255–257[c]	87[d]	$C_{19}H_{12}BrCl_2NO_4$

[a] All melting points occurred with decomposition. [b] Satisfactory analyses (C, H, N) were supplied for all of these compounds: Ed. [c] Yellow-green powder. [d] Yield of bromide. [e] Yellow microcrystals. [f] Pale green powder.

that electrophilic attack has occurred at the 9 position of the pyrido[2,1-*a*]isoindole system.

Sulfonation of **2** occurs in fuming sulfuric acid, affording a purple betaine presumably with the sulfo group at position 9, although it can be said definitely only that it has no substituent at position 6.

Attempts to carry out catalytic reduction of pyrido[2,1-*a*]isoindolium bromide (**2a**) over 10% palladium/charcoal at atmospheric pressure failed, but over platinum oxide in the presence of hydrobromic acid the aromatic rings were completely reduced, affording the dodecahydro derivative which was isolated as the methiodide **14**.



14

Experimental Section

Analyses were carried out by Janssen Pharmaceutica, Beerse, Belgium, and by Galbraith Laboratories, Knoxville, Tenn. Melting points were taken with the Hoover melting point apparatus and are uncorrected. All nmr data were obtained with 60-MHz instruments.

Pyrido[2,1-*a*]isoindolium Bromide (2a).[3]—A Hanovia 450-W water-cooled ultraviolet source was used as before, but the procedure was modified to permit preparation of **2a** on a larger scale. A Vycor rather than Pyrex filter and a more concentrated solution of **1a**, 5 g in 400 ml of 5% HBr, was used while a stream of nitrogen was bubbled through the solution during irradiation. The gray product crystallized once from ethanol–acetone (92% yield), mp 199–203° dec (lit.[3] 207.5–209.5°), was pure enough for subsequent reactions.

2-Bromo-1-(2,5-dichlorobenzyl)pyridinium Bromide (1c).—The quaternization of 2-bromopyridine with 2,5-dichlorobenzyl bromide was carried out as usual[3] except that it was at 60° for 12 days, mp 150–152° (30% yield). The colorless microcrystalline analytical sample, mp 153–154.5°, was crystallized from methanol–ethyl acetate.

Anal. Calcd for $C_{12}H_9Br_2Cl_2N$: C, 36.22; H, 2.28; N, 3.52. Found: C, 35.93; H, 2.25; N, 3.54.

7,10-Dichloropyrido[2,1-*a*]isoindolium Bromide (2c).—The photocyclization of **1c** was carried out (75% yield) by the general procedure[3] except that 5% hydrobromic acid was solvent. It crystallized from methanol–ethyl acetate as a tan powder with decomposition at about 275°.

Anal. Calcd for $C_{12}H_8BrCl_2N$: C, 45.46; H, 2.54; N, 4.42. Found: C, 45.03; H, 2.54; N, 4.19.

7,10-Dichloropyrido[2,1-*a*]isoindole (3c).—This base (mp 100–102°) was obtained (93% yield) from **2c** by addition of sodium carbonate and on sublimation at 90° (0.35 mm) afforded yellow needles: mp 102.5–104° dec; uv max (95% EtOH) 446 mμ (log ε 2.54), 420 (2.80), 395 (2.90), 370 (3.59), 354 (3.51), 281 (3.49), 246 (4.14), 213 (4.28).

Anal. Calcd for $C_{12}H_7Cl_2N$: C, 61.04; H, 2.99; N, 5.93. Found: C, 60.96; H, 2.96; N, 5.78.

6-Benzylidenepyrido[2,1-*a*]isoindolium Bromide (4).—One gram of the salt **2** was placed in about 25 ml of absolute ethanol with 1 g (excess) of the aryl carboxaldehyde. The mixture was refluxed for about 20 hr and then the solvent was removed by vacuum evaporation. The benzylidene derivatives **4** were crystallized from methanol–ethyl acetate to which, in the case of the 9-bromo derivatives **4c–e**, a trace of hydrobromic acid was added.

The **perchlorates** were prepared by addition of excess 35% perchloric acid to the aqueous solution of the bromides and crystallized from ethanol. The results are summarized in Table I.

Betaine of 6-Benzoylpyrido[2,1-*a*]isoindole (5) by Benzoylation of 2a. A. With Benzoyl Chloride.—A suspension of 0.5 g of **2a** in 5 ml of benzoyl chloride was heated on a steam bath for 4 hr. The mixture was poured into dry ether and the solid residue collected and washed with dry ether. The residue was crystallized from ethanol–water, affording 0.3 g (55%) of fluffy yellow needles: mp 135–137° (pure, mp 136–138°); uv max (95% ethanol) 419 (log ε 4.40), 405 sh (4.21), 295 sh (4.11), 286 (4.17), 272 sh (4.18), 268 (4.20), 248 (4.53), 240 (4.54), 219 (4.34), 206 (4.33).

B. With Benzoic Anhydride.—A mixture of 1 g of **2a** and 5 g of benzoic anhydride was heated for 19 hr at 100° in a stoppered flask. The solution was cooled and poured into anhydrous ether. The ether was decanted and the dark colored product taken up in chloroform; the washed and dried chloroform solution was chromatographed over alumina. The chloroform was removed and the residue crystallized from ethanol–water, affording 0.56 g (52%) of orange needles, mp 135–137°, identical (ir) with the product of procedure A.

Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.74; H, 4.83; N, 5.16.

Hyrolysis of the Betaine 5.—A suspension of 0.25 g of the betaine **5** in 10 ml of 12% hydrobromic acid was refluxed for 18 hr. The small quantity of colorless precipitate obtained on cooling the solution proved to be benzoic acid (ir). The filtered solution was made basic with sodium carbonate and the resulting base converted to the bromide by dissolving it in hydrobromic acid. The excess acid was removed by vacuum evaporation and the residue crystallized from ethanol–ethyl acetate. The gray-brown solid (0.11 g, 49% yield) was shown (ir) to be pyrido[2,1-*a*]isoindolium bromide (**2a**), mp 200–204°.

6-{[*p*-(Dimethylamino)phenyl]imino}pyrido[2,1-*a*]isoindolium Bromide (6a).—To a hot solution of 2 g of pyrido[2,1-*a*]isoindolium bromide in 20 ml of ethanol was added a hot solution of 1.2 g of *p*-nitroso-*N*,*N*-dimethylaniline in 10 ml of ethanol. The dark mixture was refluxed for 30 sec and allowed to stand for several hours at room temperature before it was cooled and the long, dark green needles, mp 213–216°, collected, yield 2.5 g (83%). After recrystallization from methanol–ethyl acetate, the product melted at 222.5–224° dec.

Anal. Calcd for $C_{20}H_{18}BrN_3 \cdot H_2O$: C, 60.31; H, 5.06; N, 10.55. Found: C, 60.17; H, 5.11; N, 10.15.

The **perchlorate** was dark blue, mp 228–229.5° dec.

Anal. Calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 59.81; H, 4.71; N, 10.16.

9-Bromo-6-{[*p*-(dimethylamino)phenyl]imino}pyrido[2,1-*a*]isoindolium Bromide (6b).—This was prepared essentially as was **6a**, affording (82%) a dark blue solid, mp 208–210° dec (after crystallization from methanol–ethyl acetate).

Anal. Calcd for $C_{20}H_{17}Br_2N_3 \cdot H_2O$: C, 50.34; H, 4.01; N, 8.81. Found: C, 50.72; H, 4.32; N, 8.37.

The **perchlorate** crystallized from dimethylformamide–ether as a deep purple solid, mp 250.5–252° dec.

Anal. Calcd for $C_{20}H_{17}BrClN_3O_4$: C, 50.18; H, 3.58; N, 8.78. Found: C, 50.12; H, 3.76; N, 8.86.

Ethyl *o*-2-Pyridylbenzoate (7a). A. From 6a.—A solution of 1 g of **6a** bromide in 15 ml of 3 *N* hydrochloric acid was refluxed for 3 hr. The solution was made basic by addition of sodium hydroxide and the alkaline solution washed with ether.

The aqueous solution was acidified and the water removed under reduced pressure. The residual salts were extracted several times with hot absolute ethanol which dissolved the organic salt but not the sodium chloride. The residue obtained by evaporating the ethanol was esterified by refluxing for 4 hr with 5% hydrogen chloride in absolute ethanol. After removal of the solvent under reduced pressure, the product was taken up in water which was then made basic by addition of sodium carbonate. The product was extracted with ether and the solution was washed, dried (Na_2SO_4), and concentrated. The residue was crystallized from petroleum ether (30–60°), affording 0.5 g (85%) of tan solid, mp 68–70°. A colorless analytical sample, mp 69.5–71°, was obtained by vacuum sublimation.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.65; H, 6.09; N, 6.00.

B. From 2-o-Tolypyridine (8).—To a refluxing suspension of 1 g of 2-*o*-tolylpyridine[12] (**8**) in 50 ml of 10% sodium hydroxide, 2.82 g of powdered potassium permanganate was added slowly over 1 hr. The mixture was stirred and refluxed for a total of 5 hr, after which the excess permanganate was destroyed by addition of ethanol. The manganese dioxide was removed by filtration and unreacted tolypyridine removed by extraction with ether. Acidification of the aqueous solution with hydrochloric acid followed by vacuum evaporation left a mixture of salts which was treated with absolute ethanol, and the procedure was continued essentially as in part A. The product, mp 69–72° (32.5% yield), was identical (mixture melting point, ir) with that obtained in part A.

2-(5′-Bromo-2′-carbethoxyphenyl)pyridine (7b).—Starting with **6b** and using the procedure for conversion of **6a** to **7a**, **7b** was produced in 50% yield, mp (after sublimation) 50–51.5°.

Anal. Calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58. Found: C, 55.09; H, 3.92; N, 4.47.

6-(Phenylazo)pyrido[2,1-*a*]isoindolium Bromide (10a).—A solution containing 0.8 g of aniline in 10 ml of 12% hydrobromic acid was cooled in an ice bath while a solution containing 0.6 g of a solution of 2 g of **2a** in 25 ml of water was added slowly. Next 8 g of sodium acetate in 25 ml of water was added slowly and the red azo compound began to precipitate. The mixture was stirred for an additional hour before collecting the precipitate, 2.25 g (80%) of dark red solid, mp 201–205° dec. The analytical sample crystallized from methanol–ethyl acetate as red needles, mp 222–223° dec.

Anal. Calcd for $C_{18}H_{14}BrN_3 \cdot 0.75H_2O$: C, 59.11; H, 4.27; N, 10.49. Found: C, 59.36; H, 4.61; N, 10.91.

The **perchlorate** crystallized from dimethylformamide–methanol as dark red needles, decomposition at 230°.

Anal. Calcd for $C_{18}H_{14}ClN_3O_4$: C, 58.15; H, 3.80; N, 11.30. Found: C, 58.13; H, 3.92; N, 10.93.

6-[(*p*-Nitrophenyl)azo]pyrido[2,1-*a*]isoindolium Perchlorate (10b).—The coupling of **2a** with diazotized *p*-nitroaniline was carried out as in the preparation of **10a**. A notable difference is that the product which separated during the sodium acetate addition because of its dark blue color appeared to be the base **9b** (100%, mp 240–248° dec) rather than the salt **10b**. The salt **10b** was formed by heating the base with dilute perchloric acid and was recrystallized from dimethylformamide as a yellow brown solid, mp 313–314° dec.

Anal. Calcd for $C_{18}H_{13}ClN_4O_6$: C, 51.87; H, 3.14; N, 13.44. Found: C, 51.70; H, 3.28; N, 13.16.

Betaine of 6-[(*p*-Sulfophenyl)azo]pyrido[2,1-*a*]isoindolium Hydroxide (10c).—The coupling reaction between **2a** and diazotized sulfanilic acid was carried out essentially as in the preparation of **10a**. The product (89% yield) was an orange powder, mp 325–326° dec, which was very insoluble and was purified only by washing with hot dimethylformamide.

Anal. Calcd for $C_{18}H_{13}N_3O_3S \cdot 0.5H_2O$: C, 59.99; H, 3.92; N, 11.66. Found: C, 59.94; H, 3.57; N, 11.78.

6-Picrylpyrido[2,1-*a*]isoindole (11).—Solutions containing 1 g of **2a** in 30 ml of water, 1 g of picryl chloride in 30 ml of chloroform, and 1.1 g of potassium carbonate in 15 ml of water were mixed in the stated order with vigorous stirring. After 1 hr of stirring at room temperature the mixture was cooled and the product collected. The resulting black powder was washed with methanol–ether (1:4) affording 1.25 g (83%), mp 147–154° with violent decomposition. The analytical sample crystallized from dioxane–ether as a very dark blue powder, exploding at 150°: uv max (EtOH–CH_3CN, 3:2) 460 mμ (log ε 3.96), 358 (3.95), 344 (3.99), 241 (4.65).

Anal. Calcd for $C_{18}H_{10}N_4O_6$: C, 57.17; H, 2.66; N, 14.81. Found: C, 57.12; H, 2.99; N, 14.87.

9-Nitropyrido[2,1-*a*]isoindole (3d).—A mixture of 10 ml of concentrated nitric acid and 10 ml of concentrated sulfuric acid was maintained below 5°, while 2 g of **2a** was added slowly. After the mixture had stood an additional 2 hr at 0° it was poured on 100 g of ice and a small quantity of bisulfite was added to destroy any free bromine. After the ice had melted the mixture was filtered and the product precipitated by addition of a solution of 100 g of sodium acetate in 200 ml of water. The product was collected and dried under vacuum, yielding 1.50 g (88%) of a burgundy powder, mp 146–148° dec. The analytical sample, purified by vacuum sublimation, had mp 149–151° dec; uv max (95% EtOH) 482 mμ (log ε 3.30), 393 (3.18), 325 sh (3.40), 295 (4.09), 270 sh (4.04), and 209 (4.25); ir (KBr) 1325 and 1515 cm^{-1} (NO_2); nmr (CF_3COOH) δ 6.25 (s, 2, CH_2), 8.00–8.90 (m, 6, aromatic), 9.27 (d, 1, H at C-4).

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.10; H, 3.62; N, 13.23.

9-Nitropyrido[2,1-*a*]isoindolium Perchlorate (2d).—The salt crystallized from acidic ethanol as a dark violet solid, with decomposition at 235–237° (darkens at 180°): uv max (95% EtOH) 325 mμ (log ε 3.90), 312 (3.99), 274 sh (3.67), 264 (3.70), 255 sh (3.66), 233 sh (3.69), and 207 (3.93).

Anal. Calcd for $C_{12}H_9ClN_2O_6$: C, 46.10; H, 2.90; N, 8.96. Found: C, 46.26; H, 2.91; N, 8.92.

6-{[*p*-(Dimethylamino)phenyl]imino}-9-nitropyrido[2,1-*a*]isoindolium Perchlorate (6c).—The crude perchlorate **2d** from 1 g of the nitro base **3d** was allowed to react with *p*-nitroso-*N*,*N*-dimethylaniline essentially as in the preparation of **6a**, affording 1.8 g (81%) of very deep purple solid, mp 244–246° dec. The analytical sample, mp 252–253° dec, was crystallized from dimethylformamide–ethyl acetate: uv max (95% EtOH) 396 mμ (log ε 4.03), 300 sh (4.12), 256 (4.37).

Anal. Calcd for $C_{20}H_{17}ClN_4O_6$: C, 54.00; H, 3.85; N, 12.60. Found: C, 54.21; H, 3.80; N, 12.61.

1-Methyl-2-(2-carbomethoxy-5-nitrophenyl)pyridinium Iodide (12).—The hydrolysis and esterification of a suspension of 1.5 g of the dimethylaminophenylimino derivative **6c** were carried out as in the preparation of **7a** except that methanol instead of ethanol was used for the esterification step. The product, unlike **7a** and **7b**, could not be recrystallized and was taken up in 40 ml of acetone containing 3 ml of methyl iodide, and the mixture was refluxed for 19 hr. The salt **12** was isolated by addition of ether, 0.75 g (55%), and recrystallized from methanol–ethyl acetate as a yellow microcrystalline solid: mp 218–220° dec; ir (KBr) 1350, 1525 cm^{-1} (NO_2); nmr (deuteriodimethyl sulfoxide) δ 3.75 (s, 3, $COOCH_3$), 4.02 (s, 3, NCH_3), 7.90–8.43 (m, 3, Ar), 8.55–9.00 (m, 3, Ar), 9.30 (d, 1, H at C-6).

Anal. Calcd for $C_{14}H_{13}IN_2O_4$: C, 42.02; H, 3.27; N, 7.00. Found: C, 42.51; H, 3.21; N, 6.98.

1-Methyl-2-(5-amino-2-carbomethoxyphenyl)piperidine Hydriodide (13).—A solution of 0.339 g of **12** in 100 ml of ethanol was stirred with 0.21 g of platinum oxide at room temperature and under hydrogen at 1-atm pressure. The theoretical quantity of hydrogen was absorbed in 1.5 hr. After filtration and concentration of the solution the residue was made to crystallize by addition of ether. The yellow microcrystals, 0.15 g (47%), mp 183–185° dec, were quite pure: ir (KBr) 835, insignificant 680–750 cm^{-1} (two adjacent H atoms); nmr (deuteriodimethyl sulfoxide, aromatic only) δ 7.00 (d of d, 1, J_{AB} = 8 Hz, J_{BX} = 2 Hz), 7.20 (d, 1, J_{BX} = 2 Hz), 7.55 (d, 1, J_{AB} = 8 Hz).

Anal. Calcd for $C_{14}H_{21}IN_2O_2$: C, 44.69; H, 5.63; N, 7.45. Found: C, 44.54; H, 5.56; N, 7.48.

Sulfonation of Pyrido[2,1-*a*]isoindolium Bromide (2a).—To 15 ml of 20% fuming sulfuric acid cooled in an ice bath 2 g of **2a** was added with stirring. When addition was complete the reaction was allowed to continue at 0° for 2 hr, after which the mixture was slowly poured into 100 ml of cold anhydrous ether. The solid was collected, washed with ether, and then crystallized from water as purple solid. Concentration of the aqueous solution and addition of ethanol caused additional precipitation.

(12) C. K. Bradsher and J. B. Moser, *J. Amer. Chem. Soc.*, **81**, 1941 (1959).

A total of 1.2 g (60%) of product, mp >400°, was obtained. The product appeared to be the betaine of sulfopyrido[2,1-*a*]isoindolium hydroxide: uv max (H_2O) 306 mμ (log ε 4.08), 252 (4.19), 244 (4.21); nmr (CF_3COOH) δ 6.10 (s, 2, CH_2), 7.87–9.05 (m, 6 Ar), 9.15 (d, 1, C-4 H).

Anal. Calcd for $C_{12}H_9NO_3S$: C, 58.29; H, 3.67; N, 5.66. Found: C, 58.20; H, 3.77; N, 5.56.

Dodecahydropyrido[2,1-*a*]isoindole Methiodide (14).—A solution of 1 g of **2a** in 100 ml of ethanol containing 2 ml of 48% hydrobromic acid was stirred with 0.5 g of platinum oxide for 4.5 hr under 1 atm of hydrogen. The calculated volume of hydrogen was absorbed. The filtered solution was concentrated, dilute sodium hydroxide added, and the amine extracted with ether. The dried ($MgSO_4$) ethereal solution was concentrated and the oily residue taken up in acetone containing 3 ml of methyl iodide. The mixture was refluxed for 18 hr and then concentrated and ether added, affording 0.85 g (66%) of colorless powder, mp 192–195° dec. It was recrystallized from methanol–ethyl acetate as microcrystals: mp 197–199° dec; nmr (D_2O) δ 2.22 (d, 14), 2.92–3.55 (m, 2), 3.67 (s, 3), 3.88–4.45 (m, 5).

Anal. Calcd for $C_{13}H_{24}IN$: C, 48.60; H, 7.53; N, 4.36. Found: C, 48.23; H, 7.36; N, 4.24.

Registry No.—**1c**, 28901-35-1; **2c**, 28901-36-2; **2d** perchlorate, 28901-37-3; **3c**, 28901-38-4; **3d**, 28901-39-5; **5**, 28901-47-5; **6a** bromide, 28901-48-6; **6a** perchlorate, 28841-17-0; **6b** bromide, 28901-49-7; **6b** perchlorate, 28901-50-0; **6c** perchlorate, 28901-51-1; **7a**, 28901-52-2; **7b**, 28901-53-3; **10a** bromide, 28901-54-4; **10a** perchlorate, 28901-55-5; **10b** perchlorate, 28901-56-6; **10c**, 28901-57-7; **11**, 28901-58-8; **12**, 28901-59-9; **13**, 28901-60-2; **14**, 28901-61-3; betaine of sulfopyrido[2,1-*a*]isoindolium hydroxide, 28883-86-5.

The Effect of Tetramethylethylenediamine on the Metalation of *N*-Methyl- and *N*-Phenylbenzylamine with *n*-Butyllithium. Deuteration and Electrophilic Condensations of Intermediate Lithioamines. Cyclodehydrations to Give N-Substituted Isoindolines[1]

Robert E. Ludt*[2a] and C. R. Hauser[2b]

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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N-Methylbenzylamine underwent dimetalation with *n*-butyllithium–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine-(TMEDA) predominantly at the nitrogen and the *o*-benzyl positions as evidenced by deuteration studies. The intermediate dilithioamine (**2**) was condensed with benzophenone, benzaldehyde, cyclohexanone, acetophenone, and propiophenone. The resulting *o*-carbinolamines from the benzophenone and benzaldehyde condensations underwent acid-catalyzed cyclodehydration to form *N*-methylisoindoline derivatives, while the ortho condensation products from the latter three ketones underwent acid-catalyzed linear dehydration reactions, rather than cyclodehydration to form isoindolines. *N*-Phenylbenzylamine was similarly dimetalated at the nitrogen and *o*-benzyl positions with TMEDA-activated *n*-butyllithium. *o*-Carbonyl addition reactions of the dilithioamine intermediate with carbon dioxide, benzophenone, benzaldehyde, and 9-fluorenone resulted in an acid and *o*-carbinolamines, which were readily cyclodehydrated to *N*-phenylphthalimidine and *N*-phenylisoindoline derivatives.

Many aromatic compounds having a nitrogen attached either on or α to the aromatic nucleus have been shown to undergo selective ortho[3] or lateral[4] metalation with *n*-butyllithium. However, there are relatively few instances of successful ring metalation of secondary amines[5] with the exception of the dilithiation of phenothiazine[6] and its benzo derivatives[7] which proceeded in good to excellent yields. Thus, the discovery that certain tertiary amines greatly increase the activity of *n*-butyllithium offers a new approach in the investigation of the metalation of secondary amines.[8–10]

In the present investigation the metalation of *N*-methyl- and *N*-phenylbenzylamine was studied. First, the sites of dimetalation in the respective amines were determined by quenching the intermediate lithioamines with deuterium oxide. Secondly, the extent of dimetalation in these two amines using *n*-butyllithium *vs.* metalations using *n*-butyllithium–TMEDA was compared by condensing the dilithio intermediates with various electrophilic compounds. Finally, the transformations of the *o*-benzyl addition products to N-substituted isoindolines was investigated.

Metalation of N-Substituted Benzylamines. Deuteration with Deuterium Oxide.—The metalation of *N*-methylbenzylamine (**1**) and *N*-phenylbenzylamine (**3**) was attempted using *n*-butyllithium and/or *n*-butyllithium–TMEDA. Determination of the sites and qualitative estimation of the extent of dimetalation in amines **1** and **3** under the various metalating conditions were accomplished by observing the positions of deuterium incorporation on quenching with deuterium oxide and examining the ir and nmr spectra of the deuterated samples.

This method of analysis indicates that dimetalation of amine **1** must occur predominantly at the nitrogen and in the ring, ortho to the *N*-methylamino group, because each ir spectrum of deuterated amine **1**, which was shown by integration of the corresponding nmr spectrum to have 0.8–1.2 D in the aromatic ring, ex-

(1) (a) Supported by the Army Research Office (Durham) and by the National Institute of Health Grant No. CA 04455-11 from the National Cancer Institute. (b) This work represents part of the research of R. E. L., partially fulfilling the requirements for the degree of Doctor of Philosophy at Duke University.

(2) (a) Department of Chemistry, Virginia Military Institute, Lexington, Va. 24450; (b) Deceased, Jan 6, 1970.

(3) (a) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963); (b) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963); (c) A. R. Lepley, W. A. Khan, A. B. Guimanini, and A. G. Guimanini, *ibid.*, **31**, 2047 (1966).

(4) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **29**, 1387 (1964).

(5) (a) H. Gilman, G. E. Brown, F. J. Webb, and S. M. Spatz, *J. Amer. Chem. Soc.*, **62**, 977 (1950(; (b) H. Gilman and L. A. Woods, *ibid.*, **66**, 33 (1943); (c) R. T. Hawkins and D. B. Stroup, *J. Org. Chem.*, **34**, 1173 (1969).

(6) H. Gilman, D. A. Shirley, and P. R. VanEss, *J. Amer. Chem. Soc.*, **66**, 625 (1944).

(7) D. A. Shirley and J. C. Gilmer, *J. Org. Chem.*, **27**, 4421 (1962).

(8) (a) J. F. Eastham and C. G. Screttas, *J. Amer. Chem. Soc.*, **87**, 3276 (1965); (b) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964).

(9) R. West and P. C. Jones, *J. Amer. Chem. Soc.*, **90**,2656 (1968).

(10) R. E. Ludt, G. P. Crowther, and C. R. Hauser, *J. Org. Chem.*, **35**, 1288 (1970).

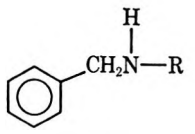
TABLE I

METALATION OF N-METHYLBENZYLAMINE (1) USING n-BUTYLLITHIUM AND n-BUTYLLITHIUM–TMEDA. DEUTERATION OF INTERMEDIATE LITHIOAMINES WITH DEUTERIUM OXIDE

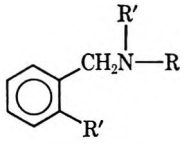
Expt no.	Ratio of n-C_4H_9Li/1	Solvent (metalation procedure)	Metalation time	No. of D atoms incorporated—Lateral	No. of D atoms incorporated—Ortho
1	2.1:1	Hexane–TMEDA (direct)[d]	5 min	0.32–0.39	0.6–0.64
2[c]	2.1:1	Hexane–TMEDA (direct)	25 min	0.47	0.77–0.85
3[a,b]	2.1:1	Hexane–TMEDA (direct)	20 hr	0.08	0.99
4	1:1; 1.1:0	Hexane–TMEDA (two-step)[d]	30–60 min; 3 hr	0.12	0.88
5[a,b]	2.1:1	Ether–TMEDA	5 hr	0.13	1.2
6[a,b]	2.5:1	Hexane–TMEDA (indirect)[d]	1.5 hr	0.06–0.19	0.97
7[a,b]	2.5:1	Hexane–TMEDA (indirect)	25 min	0.16	1.01

[a] Observed 1,2-disubstituted absorption band in ir spectrum of deuterated sample. [b] Distinct absorption band near 2230 cm^{-1} in ir spectrum assigned to ring deuterium. [c] Small absorption band near 2230 cm^{-1} in ir spectrum assigned to ring deuterium. [d] See Experimental Section for definition of these terms.

hibited strong 1,2-disubstitution absorption bands in the 600–800-cm^{-1} region and a strong N–D absorption band.[11] However, the site and extent of metalation in amine **1** apparently depend upon two factors: (1) the method of mixing the lithium reagent and the secondary and tertiary amines, and (2) the period of metalation.



1, R = CH_3
3, R = C_6H_5

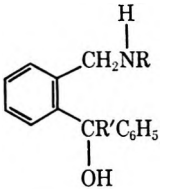


2, R = CH_3; R′ = Li
4, R = C_6H_5; R′ = Li
5, R = C_6H_5; R′ = D

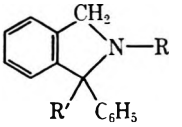
Unlike the results with amine **1**, this method of deuterium analysis cannot conclusively determine the sites of dimetalation in amine **3**, since the data obtained in this case cannot eliminate the possibility that ring metalation of **3** had occurred in the *N*-phenyl ring rather than in the *o*-benzyl position. The deuteration study of metalated **3** does indicate (1) that dimetalation of **3** occurs, presumably to form dilithioamine **4**, (2) that this dimetalation proceeds in much higher yield and in a shorter time using TMEDA-activated *n*-butyllithium than in the metalation using *n*-butyllithium alone, and (3) that the formation of **4** proceeds more satisfactorily using the indirect rather than the direct metalation procedure.

An unexpected finding was the apparent difference in the amount of ring deuterium incorporation which was observed when metalation of **3** was effected in ether and in hexane. Thus, in contrast to *N*-methylbenzylamine (**1**) where ortho metalation and subsequent condensation (see below) were found to proceed best in ether–hexane, deuteration of **4** suggests that the best conditions for effecting ortho metalation of *N*-phenylbenzylamine would be in hexane alone.

Metalation of *N*-Methylbenzylamine to Form Lithioamine 2. Condensation with Various Electrophilic Reagents.—The results of the deuteration study suggest that dilithioamine **2** could be prepared using TMEDA-activated *n*-butyllithium in either ether–hexane or hexane alone (*cf.* Table I; expt 5 and 6). In both of these instances, the ring (ortho) to α-deuterium incorporation ratio was nearly 10:1. To determine whether these two methods of metalation could be applied with equal success to synthetic problems, dilithioamine **2** was prepared under these conditions and then condensed with benzaldehyde and benzophenone. The results of these condensation reactions, summarized in Table II, show that the yields of benzophenone adduct (**6**) and benzaldehyde adduct (**7**) expected from the extent of deuterium incorporation in amine **1** were not realized. However, these results do show (1) that TMEDA–*n*-butyllithium is a more efficient metalating reagent of amine **1** than is *n*-butyllithium alone (*cf.* Table II; expt 1 and 4) and (2) that condensation reactions of dilithioamine **2** generally proceed more satisfactorily when **1** is metalated using TMEDA-activated *n*-butyllithium in ether–hexane rather than in hexane alone. This latter finding is of added interest since some workers have found that TMEDA-activated *n*-butyllithium metalations of benzene and toluene do not occur satisfactorily in ether.[8,9]



6, R = CH_3; R′ = C_6H_5
7, R = CH_3; R′ = H



8, R = CH_3; R′ = C_6H_5
9, R = CH_3; R′ = H
21, R = R′ = C_6H_5
22, R = C_6H_5; R′ = H

Chemical verification that ortho ring metalation of amine **1** was occurring was afforded by the acid-catalyzed cyclodehydration of **6** to form 1,2-diphenyl-2-methylisoindoline (**8**). This cyclization was effected by refluxing **6** in either 20% sulfuric acid or 48% hydrobromic acid for 2–4 hr. Attempts to cyclize **6** with either concentrated sulfuric acid at 0°,[12] or with 5%

(11) Deuterium atom is known to act as any substituted functional group in determining the absorption pattern of an aromatic compound in the 690–990-cm^{-1} region: G. V. D. Tiers, *J. Chem. Phys.*, **20**, 761 (1952).

(12) C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6** 475 (1969).

TABLE II

METALATION OF *N*-METHYLBENZYLAMINE (1). CONDENSATION OF THE INTERMEDIATE LITHIOAMINE WITH BENZOPHENONE[a] AND BENZALDEHYDE[a] TO FORM CARBINOLAMINES 6 AND 7, RESPECTIVELY

Expt no.	Ratio of *n*-C_4H_9Li/1	Lithiating reagent	Solvent	Metalation time, hr	% yield of 6	% yield of 7[b]
1[c]	2.1:1	*n*-C_4H_9Li–TMEDA (4:1)	Ether–hexane	5	48–52	63[g]
2[d]	2.5:1	*n*-C_4H_9Li–TMEDA (4:1)	Hexane	1.5	35–42	64
3[e]	1.1:1; 1.1:0	*n*-C_4H_9Li; *n*-C_4H_9Li–TMEDA (1:0; 3:1)	Ether–hexane	1; 3	15–20	48–53
4	2.1:1	*n*-C_4H_9Li	Ether–hexane	48	46–48[f]	55[g]

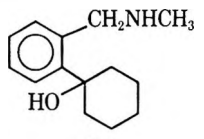
[a] The ratio of amine 1 to benzophenone was 1:2 in each condensation reaction; the ratio of 1 to benzaldehyde was 1:1.5 in each reaction. [b] Interestingly, the nmr spectrum of 7 contained an AB quartet which was assigned to the methylene protons. Nonequivalent as a result of the asymmetric carbon at the ortho position in 7: C. J. Nelson, M.A. Thesis, Duke University, 1965. Similar AB patterns have been observed in the nmr spectra of the ortho condensation products of dimethylbenzylamine: J. C. Randall, J. J. McLeskey, III, P. Smith, and M. E. Hobbs, *J. Amer. Chem. Soc.*, 86, 3229 (1964); see also Nelson, this footnote. [c] The *n*-butyllithium was added to an ether solution of amine 1 and TMEDA. [d] The indirect metalation procedure was used. [e] A two-step metalation procedure was used. [f] Unpublished preliminary work in these laboratories on the metalation of secondary amines using *n*-butyllithium alone was done by R. L. Gay, R. L. Vaulx, and F. N. Jones. [g] In addition to recovered amine 1, up to 10% yield of diadduct 10 was isolated under these reaction conditions.

sulfuric acid in acetic acid at room temperature,[13] failed.

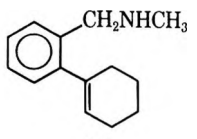
Benzaldehyde adduct **7** underwent a similar cyclodehydration reaction when refluxed for 2 hr in 48% hydrobromic acid. Attempted cyclization with refluxing 20% sulfuric acid gave only recovered carbinolamine **7**.

Using TMEDA–*n*-butyllithium in ether–hexane as the metalating conditions, dilithioamine **2** was also successfully condensed with cyclohexanone, acetophenone, and propiophenone to give carbinolamines **12**, **13**, and **14**, respectively. In each of these condensation reactions, better yields of the carbinols were realized at 0 or −80° than at room temperature.[14]

When carbinols **12**, **13**, and **14** were subjected to the same acid-catalyzed reaction conditions which converted **6** and **7** to isoindolines **8** and **9**, there was no evidence that any cyclized products had been produced. Instead, these carbinolamines underwent linear dehydration, rather than cyclodehydration, to form olefin amines **15**, **16**, and **17**, respectively; the linear dehydration of carbinol **14** afforded a mixture of geometrical isomers, as evidenced by the complex nmr spectrum of **17**. It thus appears that isoindoline formation occurs only when linear dehydration cannot occur.



12



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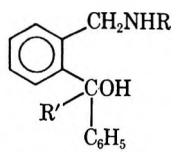
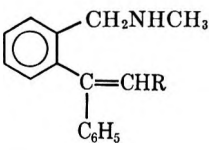
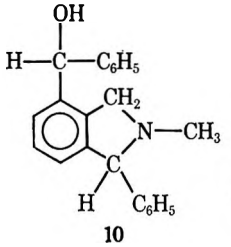


13, R = R′ = CH_3
14, R = CH_3; R′ = C_2H_5
18, R = R′ = C_6H_5
19, R = C_6H_5; R′ = H
24, R = C_6H_5; R = CH_3

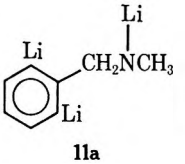


16, R = H
17, R = CH_3(*cis* and *trans*)

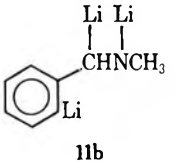
While the condensation reactions of **2** with benzophenone, acetophenone, propiophenone, and cyclohexanone proceeded in much better yield in ether–hexane than in hexane alone, there was no significant difference in yield of benzaldehyde adduct **7** using the different solvent systems (*cf.* Table II; expt 1 and 2). Of additional synthetic interest was the observation that, when amine **1** was metalated with a large excess of TMEDA-activated *n*-butyllithium (2.5–2.7 equiv), using the direct metalating procedure (in hexane), and then condensed with excess benzaldehyde, the 2,6 diadduct was isolated as the cyclized product **10**, which showed strong absorption bands at 762 and 740 cm^{-1}, characteristic of 1,2,3 trisubstitution, and a clear two-proton benzylic methylene AB quartet (J_{obsd} = 14 Hz) centered at δ 4.5 in the nmr spectrum. Whether the cyclization of this adduct occurred under the reaction conditions or during work-up procedures has not been ascertained.



10



11a



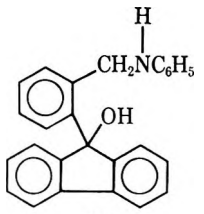
11b

It should be noted that, while **10** was the major isolated product using a large excess of the lithium reagent in hexane, this diadduct was also isolated in varying yields as a minor product when other metalation procedures were employed in the benzaldehyde condensation reaction (*cf.* Table II; footnote *g*).

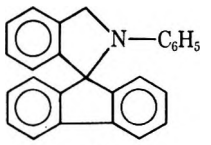
The isolation of diadduct **10** in 55–57% yield has two significant implications. First, it apparently represents the first such 2,6-dicondensation adduct isolated in the metalation of a benzylamine, although a similar dicondensation was previously observed in the metalation of *N*,*N*,*N*′,*N*′-tetramethyl-*p*-xylenediamine using excess *n*-butyllithium in ether in which some 2,5-disubstituted benzophenone adduct was isolated, along with the mono-2-substituted derivative.[15] In the second place, the isolation of diadduct **10** suggests that a trilithioamine intermediate, conceivably either **11a** or **11b**, is formed in the metalation of amine **1** using excess TMEDA-activated *n*-butyllithium.

(13) A. Gandini and P. H. Plesh, *J. Chem. Soc.*, **3**, 6019 (1965).
(14) G. Wittig, W. Boll, and H. H. Kruch, *Chem., Ber.*, **95**, 2514 (1962).
(15) G. P. Crowther, Ph.D. Dissertation, Duke University, 1967.

Carbonation and Carbonyl Addition Reactions of Lithioamine 4. Cyclodehydration of the Resulting Ortho Derivatives.—Dilithioamine **4** was prepared using TMEDA-activated *n*-butyllithium in hexane and then condensed with benzophenone, benzaldehyde, and 9-fluorenone to form carbinolamines **18**, **19**,[16] and **20**, respectively, in good to excellent yields. The near-quantitative yield of **20** observed, even when only 1 equiv of ketone was employed, suggests that quantitative metalation of amine **3** must occur during the 1.5-hr metalation period, since related results in these laboratories have shown that excess *n*-butyllithium will react competitively with the lithioamine for the electrophilic compound.



20

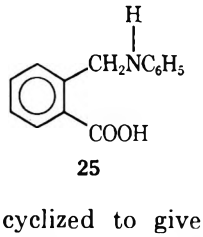


23

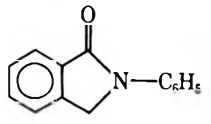
Chemical confirmation that metalation of amine **3** had occurred in the benzyl ring to form **4**, rather than in the *N*-phenyl ring, was obtained by the acid-catalyzed cyclodehydration of **18**, **19**, and **20** to form isoindolines **21**, **22**, and **23**, respectively.

While the condensations of **4** with benzophenone, benzaldehyde, and 9-fluorenone proceeded in excellent yields, attempted condensations of dilithioamine **4** with either cyclohexanone or acetophenone were unsuccessful; some carbonyl addition of **4** and acetophenone did occur, for a 10% yield of **24** was isolated in this condensation along with 65–75% of recovered amine **3**.

Carbonation of **4** afforded 61–65% of *o*-(*N*-phenylaminomethyl)benzoic acid (**25**) along with a 10% yield of phthalimidine (**26**). Amino acid **25** was thermally cyclized to give 2-phenylphthalimide (**26**) in 90% yield. The isolation of **26** from the thermal cyclization of carbonated amine further confirms that metalation of amine **3** occurs ortho to the *N*-phenylaminomethyl group.



25



26

Discussion

The preceding results have shown that metalations of certain secondary benzylamines occur more efficiently using TMEDA-activated *n*-butyllithium than in metalations using *n*-butyllithium alone. Secondly, many of the *o*-carbonyl addition products were successfully converted to N-substituted isoindolines, thus providing a simple two-step procedure for converting N-substituted benzylamines to N-substituted isoindoles.

Each of the isolated products was identified by absorption spectra and/or by comparison of physical properties with those of known compounds. Of particular interest were the nmr spectra of isoindolines **9** and **22**, which afford good examples of long-range ABC spin coupled systems. (Similar long-range coupling has been observed previously in other isoindoline systems.[17]) The available evidence suggests that such long-range coupling over four bonds is observable only when nuclei lie in a favorable geometrical arrangement ("M" or "W" pattern), usually enforced by a rigid bicyclic carbon skeleton, or when an sp^2 hybridized atom intervenes between the remote protons.[18]

It was also noted that the signal for the benzylic methylene in the nmr spectra of isoindolines **22**, **23**, and **24** shifted downfield to δ 4.95. This downfield shift of the benzylic methylene from δ 2.0–4.0 in the nmr spectra of the respective carbinolamines to near δ 5.0 in the nmr spectra of the *N*-phenylisoindoline derivatives synthesized in this investigation is apparently characteristic.

Experimental Section

Melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. All boiling points are uncorrected. Elemental analyses were performed by M-H-W Laboratories in Garden City, Mich. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord using the potassium bromide pellet method for solids and sodium chloride plates for the liquids. The nmr spectra were obtained on both Varian A-60 and Varian T-60 spectrometers. All chemical shifts are reported in parts per million downfield from a tetramethylsilane (TMS) standard.

Unless otherwise stated, the metalation reactions were done in a 500-ml round-bottom flask fitted with a Claisen adapter. A dropping funnel was placed directly about the flask, and a condenser was placed in the other side of the Claisen adapter. The entire apparatus was predried and kept under a nitrogen atmosphere.

Both hexane and the ethyl ether were distilled over an appropriate drying reagent before being used as solvents in the metalation reactions.

Metalation of *N*-Methylbenzylamine Using *n*-Butyllithium–TMEDA in Ether.—A solution of 2.0 g (0.017 mol) of TMEDA and 4.0 g (0.033 mol) of *N*-methylbenzylamine in 200 ml of anhydrous ether was placed in a dry 500-ml round-bottomed flask. To this stirred solution was added 32 ml (0.071 mol) of approximately 2.25 *M* *n*-butyllithium in hexane.[19] The resulting cherry-red solution was stirred for 5–6 hr, and then treated with the appropriate electrophile.

Metalation of *N*-Methylbenzylamine Using *n*-Butyllithium and *n*-Butyllithium–TMEDA (Two-Step Procedure).—To a solution of 4.0 g (0.033 mol) of *N*-methylbenzylamine in 150 ml of dry hexane was added 16 ml (0.036 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. The resulting mixture was stirred 30–60 min at room temperature when a premixed (10–15 min) solution of 1.8 g (0.016 mol) of TMEDA and 16 ml (0.036 mol) of *n*-butyllithium was added dropwise over a 5-min period. The resulting suspension was stirred from 30 min to 3 hr and then treated with the appropriate electrophile.

Metalation of *N*-Substituted Benzylamine Using *n*-Butyllithium–TMEDA in Hexane (Direct Method).—A solution of 4.0 g (0.033 mol) of *N*-methylbenzylamine or 5.0 g (0.0273 mol) of *N*-phenylbenzylamine in 150 ml of dry hexane was placed in a dry 500-ml round-bottomed flask. To this clear solution was added a premixed solution of 1.50–6.0 g (0.0174–0.07 mol) of TMEDA and 29–44 ml (0.066–0.099 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. The resulting suspension was stirred from 1.5 to 4 hr and then treated with the appropriate electrophilic compound.

(16) Carbinolamine **19** was isolated as a viscous oil by distilling the reaction mixture under reduced pressure. A solid diacetyl derivative of **19** was obtained by refluxing the carbinolamine in acetic anhydride (see Experimental Section).

(17) (a) W. Metlesics, T. Anton, and L. H. Sternbach, *J. Org. Chem.*, **32**, 2185 (1967); (b) J. T. Gerig, *Tetrahedron Lett.*, 4625 (1967).

(18) S. Sternhell, *Quart. Rev. Chem. Soc.*, **23**, 236 (1969).

(19) Alpha Inorganic, Inc., Beverly, Mass.

Metalation of *N*-Substituted Benzylamine Using *n*-Butyllithium–TMEDA in Hexane (Indirect Method).—A solution of 1.35–3.0 g (0.0116–0.025 mol) of TMEDA in 150–200 ml of hexane was placed in a dry 500-ml round-bottomed flask. To this stirred solution was added 21–37 ml (0.046–0.82 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. After addition of the lithium reagent, stirring was continued 10–15 min (during this period a white precipitate usually formed). To this white suspension was added 4.0 g (0.044 mol) of *N*-methylbenzylamine [or 5.0 g (0.0273 mol) of *N*-phenylbenzylamine] in 60 ml of hexane. The resulting suspension was stirred for 1.5–4 hr and then treated with the appropriate electrophile.

Deuteration of Intermediate Lithioamines with Deuterium Oxide.—To the magnetically stirred suspension of the respective lithioamine was added a 2–3 *M* excess of deuterium oxide (99.8% deuterium). Stirring was continued until a clear yellow solution resulted (5–120 min). The organic layer was filtered free of the solid which had separated, dried ($MgSO_4$), and then concentrated to give the respective deuterated amine. The recovery of undistilled deuterated amines ranged from 75 to 100%. The crude liquids were fractionated at reduced pressure through a 15-cm Vigreux column [65–70° (12–13 mm) for amine 1 and 114–120° (0.1 mm) for amine 3], a midcut being collected for deuterium analysis (see Table I and below). The TMEDA employed in the metalations was distilled at atmospheric pressure (120–123°).

The nmr spectra of the deuterated amines were run either neat or in deuteriochloroform solutions. The integration data were obtained by comparing the integration areas of the signals in the nmr spectra of the deuterated samples with the analogous peaks in the nmr spectrum of undeuterated amine. For amine 1 the *N*-methyl singlet (3.0 H) was used as an internal standard. The ir spectra of the deuterated samples were taken neat.

(a) Amine 3: ir 3400 (NH), 748 and 690 cm^{-1} (monosubstituted); nmr ($CDCl_3$) δ 4.73 (s, 2, $C_6H_5CH_2$), 6.4–79 (m, 10, aromatic); ratio of aromatic/lateral = 5.0.

(b) Deuterated 3 (ether metalation): ir 3410 (NH), 2540 (ND), 752 (broad), 730 and 690 cm^{-1} (predominantly monosubstituted); nmr ($CDCl_3$) 4.1 (s, 2, $C_6H_5CH_2$), 6.4–7.4 (m, 10, aromatic); ratio of aromatic/lateral = 5.0.

(c) Deuterated 3 (hexane metalation): ir 3410 (NH), 2540 (ND), 2230 (ring D), 776, 752, and 691 cm^{-1} (combination of ortho and monosubstituted); nmr ($CDCl_3$) δ 3.91 (s, 2, $C_6H_5CH_2$), 6.3–7.8 (m, 9.17, of aromatic); ratio of aromatic/lateral = 4.6.

Carbonyl Addition Reactions of Intermediate Dilithioamines 2.[20]—The respective dilithioamines were allowed to react with benzaldehyde and the various ketones. The resulting mixtures were neutralized after 30 min–12 hr with 50–100 ml of water. The aqueous layer was separated and then washed with 50 ml of ether. In the condensations with benzophenone and benzaldehyde, the combined ether fractions were extracted with 10% HCl. The resulting acidic fractions were made basic with NaOH, thus liberating the amine which was extracted into ether–methylene chloride (1:1). The organic solution was dried ($MgSO_4$), concentrated, and then worked up as described below.

In the condensations with cyclohexanone, acetophenone, and propiophenone, the acid–base work-up was omitted.

Condensation of 2 with Benzophenone. Formation of *o*-(*N*-Methylaminomethyl)triphenylcarbinol (6).—An ether solution of 6.36 g (0.035 mol) of benzophenone was added to the solution of lithioamine 2. Following neutralization and normal work-up, hexane was added to the red liquid, and the resulting solution was cooled 10 hr and then filtered to give 5.0 g (50%) of pink-white solid, mp 172–180°. Recrystallization from absolute ethanol gave an analytical sample: mp 180–182°; ir (KBr) 3500 (OH), 3320 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.28 (s, 3, NCH_3), 3.28 (s, 1.83, $PhCH_2$).

Cyclodehydration of 6 with 48% Hydrobromic Acid. Formation of 1,1-Diphenyl-2-methylisoindoline (8).—Into a 100-ml round-bottomed flask were placed 5.0 g (0.016 mol) of carbinolamine 6 and 50 ml of 48% hydrobromic acid. This solution was refluxed 1.5–2 hr, cooled, and then made basic with 6 *N* NaOH. The basic solution was extracted three times with 100-ml portions of methylene chloride. The combined organic extracts were dried ($MgSO_4$) and then concentrated to an oil which solidified on addition of ether to give 3.37 g (70%) of isoindoline (8), mp 128–136°. Recrystallization from absolute ethanol afforded an analytical sample: mp 135–137°; ir no NH or OH; nmr ($CDCl_3$) δ 2.13 (s, 3, NCH_3), 3.93 (s, 1.95, $PhCH_2$).

Cyclodehydration of 6 with 20% Sulfuric Acid.—Into a 100-ml round-bottomed flask were placed 5.0 g (0.016 mol) of 6 and 50 ml of 20% sulfuric acid. This solution was refluxed 2–3 hr, cooled, and then poured into an aqueous NaOH solution. When cool, the basic solution was extracted with 100-ml portions of ether–methylene chloride (1:1). The combined extracts were dried ($MgSO_4$) and then concentrated to an oil which was dissolved in absolute ethanol. Cooling gave a 75–85% yield of 8, mp 133–137°.

Condensation of 2 with Benzaldehyde. Formation of *o*-(*N*-Methylaminomethyl)diphenylcarbinol (7).—An ether solution of 5.0 g (0.047 mol) of benzaldehyde was added to the solution of lithioamine 2. After neutralization and normal work-up, the resulting yellow-red liquid was distilled at slightly reduced pressure to remove the TMEDA and unracted amine 1. The higher boiling residue was then distilled, giving 4.71 g (63%) of yellow oil, bp 150–155° (0.18 mm). Further distillation afforded pure 7: bp 139–142° (0.08 mm); ir (heat) 3320 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.14 (s, 3, NCH_2), 3.30 (H_A), and 3.40 (H_B) (AB q, 1.94, $J_{AB_{app}}$ = 12 Hz, $PhCH_2$–), 5.7 (s, 0.88, >C(O–H).

Benzoylation of 7 with Benzoyl Chloride.[21]—Since attempts to crystallize 7 were unsuccessful, a solid dibenzoyl derivative was synthesized using the procedure described in ref 22 (pyridine method). Following this procedure, a 39% yield of the dibenzoyl derivative, mp 133–134°, was realized (note that recrystallization from hexane–ethanol require several days of cooling): ir (KBr) 1720 (–COO–), 1640 cm^{-1} (–CON<).

Cyclodehydration of 7 with 48% Hydrobromic Acid. Formation of 1-Phenyl-2-methylisoindoline (9).—Into a 100-ml round-bottomed flask were placed 5.35 g (0.0235 mol) of 7 and 40 ml of 48% HBr. Following the procedure described above, a yellow oil was isolated, which was distilled at reduced pressure to give 3.0 g (62%) of 9, bp 110–112° (0.14 mm); the oil solidified on standing. Recrystallization of the white crystals from hexane gave an analytical sample, mp 57–58°.

It is important to note that refluxing 7 in 20% H_2SO_4 did not effect cyclodehydration; after 3–4 hr of refluxing 7 in 20% H_2SO_4, only 7 was recovered on work-up (80–90% recovery): ir (neat) no NH or OH; nmr ($CDCl_3$) δ 2.43 (s, 3, NCH_3), 3.69 (H_A), 4.32 (H_B), 4.49 (H_C) (ABC m, 2.8, $J_{AB_{app}}$ = 14 Hz, $J_{AC_{app}}$ = 3 Hz, $J_{CB_{app}}$ = 0.7–2.1 Hz, $ArCH_CNCH_3CH_AH_BAr$).

Metalation of *N*-Methylbenzylamine with Excess *n*-Butyllithium–TMEDA. Twofold Condensation with Benzaldehyde.—A solution of 3.9 g (0.0335 mol) of TMEDA in 60 ml of hexane was placed into a dry 500-ml round-bottomed flask. To this stirred solution was added 41 ml (0.0924 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. After addition of the lithium reagent, stirring was continued 15 min; a white precipitate formed during the period. To this white suspension was added a hexane solution of 4.0 g (0.033 mol) of *N*-methylbenzylamine (the amine solution was added rapidly to the lithium reagent), and the mixture was stirred for 30 min. A solution of 7.0 g (0.066 mol) of benzaldehyde in 50 ml of hexane was added dropwise to the red-white suspension of the intermediate lithioamine. After addition of the aldehyde solution was complete, the resulting solution was stirred for 12 hr and then neutralized by adding 60 ml of water. The aqueous layer was separated and washed with 50 ml of ether. The combined organic fractions were dried ($MgSO_4$) and then concentrated to a yellow-red liquid. A solid precipitate formed on standing for 3–4 hr. This precipitate was initially triturated with hexane and filtered, yielding 6.31 g (65–75%) of white solid, mp 139–143°. Recrystallization from benzene–hexane and then absolute methanol afforded an analytical sample, mp 146–147°. It should be noted that this product was also isolated in varying yield when the other metalation procedures (see Table II) were employed in the benzaldehyde condensation reaction: ir (KBr) 3430 (OH), 762 and 740 (1,2,3 trisubstituted), 748 and 699 cm^{-1} (monosubstituted); nmr ($CDCl_3$) δ 1.93 (s, 3, NCH_3), AB q centered at 4.5 ($\Delta\nu$ = 46.6 Hz, AB q, 2, J = 15 Hz, $C_6H_5CH_2N$), 5.95 (s, 1, >CH), 6.08 (s, 1, >C(H)OH).

(20) Unless otherwise indicated, analyses were within acceptable limits for proof of structure.

(21) Solid dibenzoylated derivative of carbinolamine 7.

(22) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, p 226.

Condensation of 2 with Cyclohexanone. Formation of 1-[o-(*N*-Methylaminomethyl)phenyl]cyclohexanol (12).—A ether solution of 4.0 g (0.0408 mol) of cyclohexanone was added to the solution of lithioamine **2** precooled in a Dry Ice–acetone bath. After neutralization and normal work-up, the resulting liquid was fractionated, initially at slightly reduced pressure to remove the TMEDA and cyclohexanone. Further distillation gave 35–40% recovered amine **1**, bp 65–70° (12–13 mm), and 3.53 g (51%) of **12**, bp 125–135° (0.14 mm). On cooling and mixing with hexane, the liquid solidified. Recrystallization of **12** from benzene–hexane and then petroleum ether gave an analytical sample, mp 73–75°.

When this condensation was effected at room temperature, a 39% yield of **12** was realized: ir (neat) 3320 (NH), 757 cm^{-1} (1,2 disubstituted); nmr ($CDCl_3$) δ 1.18–2.0 (m, 10.1, cyclohexyl CH_2), 2.41 (s, 2.88, NCH_3), 3.95 (s, 1.8, $PhCH_2$).

Dehydration of 12 with 48% Hydrobromic Acid. Formation of 1-[o-(*N*-Methylaminomethyl)phenyl]cyclohexene (15).—Into a 100-ml round-bottomed flask were placed 4.4 g (0.02 mol) of **12** and 50 ml of 48% HBr. Following the procedure described previously, a light red liquid was isolated. Distillation at reduced pressure afforded 3.0–3.1 g (75–77%) of colorless liquid **15**: bp 100–103° (0.17 mm); ir (neat) 3320 (NH), 1650 and 1823 cm^{-1} (trisubstituted olefin); nmr ($CDCl_3$) δ 1.48–2.3 (m, 8, cyclohexyl CH_2), 2.3 (s, 3, NCH_3), 3.62 (s, 1.9, $PhCH_2$), 5.5 (broad s, 0.8, $-CH_2=C<$).

Condensation of 2 with Acetophenone. Formation of 1,1-[*N*-Methylaminomethyl)diphenyl]ethanol (13).—An ether solution of 4.3 g (0.036 mol) of acetophenone was added to the solution of **2**, precooled in a Dry Ice–acetone bath. After neutralization and normal work-up, the resulting liquid was fractionated as described previously to give 3.15 g (40%) of yellow-red liquid **13**, bp 140–145° (0.14 mm). Dissolving this oil in hexane–ethanol (2:1) gave a white crystalline solid, mp 96–98°, on cooling. Further recrystallization from 95% ethanol gave an analytical sample, mp 97°–98°.

When this condensation was done at room temperature, a 33% yield of **13** was realized: ir (neat) 3300 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.8 (s, 2.86, $>C(O^-)CH_3$), s, 2.9, NCH_3), 3.1 (s, 1.9, $PhCH_2$).

Dehydration of 13 with 48% Hydrobromic Acid. Formation of 1,1-[o-(*N*-Methylaminomethyl)diphenyl]ethylene (16)—Into a 100-ml round-bottomed flask were placed 3.8 g (0.057 mol) of **13** and 30 ml of 48% HBr. Following the procedure described previously, a light yellow liquid was isolated Distillation under reduced pressure gave 2.71 g (77%) of colorless liquid **16**: bp 115° (0.1mm); ir (neat) 3320 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.12 (s, 3, NCH_3), 3.51 (s, 1.9, $PhCH_2$), 5.2 (d, 1.0, J = 1.5 Hz, C=CHH), and 5.7 (d, 0.85, J = 1.5 Hz, >C=CHH).

Condensation of 2 with Propiophenone. Formation of 1,1-[o-(*N*-Methylaminomethyl)diphenyl]propanol (14)—An ether solution of 4.25 g (0.035 mol) of propiophenone was added to the solution of lithioamine **2**, precooled in an ice bath. After neutralization and normal work-up, the resulting liquid was fractionated as described previously to give 3.55 g (43%) of yellow oil **14**, bp 145–155° (0.14 mm); the oil solidified on standing. Recrystallization from ethanol–hexane gave an analytical sample: mp 93–95°; ir (neat) 3310 cm^{-1} (NH); nmr ($CDCl_3$) δ 0.8–1.2 (overlapping t and q, 4.5, J = 7 Hz, $-CH_2CH_3$), 2.3 (s, 3, NCH_3), 3.15 (s, 1.9, $PhCH_2$).

Dehydration of 14 with 48% Hydrobromic Acid. Formation of 1,1-[o-(*N*-Methylaminomethyl)diphenyl-2-methylethylene (17).—Into a 100-ml round-bottomed flask were placed 3.8 g (0.0149 mol) of **14** and 40 ml of 48% HBr. Following the procedure described previously, an orange liquid was isolated. Distillation under reduced pressure gave 2.5 g (70%) of colorless liquid **17**: bp 125–128°; ir (neat) 3305 (NH), 1595 cm^{-1} (C=C, conjugated); nmr ($CDCl_3$) δ 1.56 and 1.85 in a 3:1 ratio (2 d, 2.3, J = 7 Hz, $>C=C(CH_3)-$ (CH_3 group cis and trans)), 2.18 and 2.34 in a 3:1 ratio (2 s, 2.9, NCH_3), 3.47 and 3.70 in a 3:1 ratio (2 s, 2.0, $PhCH_2$), 6.28 (q, 0.8, J = 7 Hz, >C=CH). Presumably the product is a mixture of geometric isomers, the major isomer being present in 75–80% yield.

Anal. Calcd for C: 86.03. Found: 85.70.

Carbonyl Addition Reactions of Intermediate Dilithioamines (4).—Dilithioamine **4** was allowed to react with benzaldehyde and the various ketones. The resulting mixtures were inversely neutralized into an ether solution of acetic acid after 30 min–10 hr. After several minutes, 50 ml of water was added to the neutralized suspension. When the solid had dissolved, the aqueous layer was separated, and then washed with 50 ml of ether. The combined organic fractions were extracted with three 100-ml portions of 10% HCl; the solid HCl salt which formed was separated and then poured into an aqueous $NaHCO_3$ solution. After being stirred for 1 hr, the neutralized carbinolamine was collected by filtration. (In the benzaldehyde condensations, a viscous yellow oil was liberated on neutralization of the HCl salt. This oil was extracted into ether and then purified as described below.)

Condensation of Lithioamine 4 with Benzophenone. Formation of *o*-(*N*-Phenylaminomethyl)triphenylcarbinol (18).—An ether solution of 7.6 g (0.042 mol) of benzophenone was added to the suspension of lithioamine **4**. After the resulting mixture was stirred for 30 min–4 hr, neutralization and work-up gave 6.83 g (86%) of carbinolamine **18**, mp 149–151°. Several recrystallizations from CH_3CN afforded an analytical sample: mp 154–155.5°; ir (KBr) 3580 (OH), 3425 cm^{-1} (NH); nmr ($CDCl_3$) δ 3.95 (s, 1.9, $C_6H_5CH_2$), 5.2 (broad s, 1, OH), 5.7 (broad s, 1, NH).

Cyclodehydration of 18 with 20% Sulfuric Acid. Formation of 1,1,2-Triphenylisoindoline (21).—Into a 100-ml round-bottomed flask were placed 5.1 g (0.0143 mole) of carbinolamine **18** and 20 ml of 20% sulfuric acid. This mixture was refluxed 2–3 hr, cooled, and then poured into aqueous sodium hydroxide. After a 30-min period of stirring, the suspension was filtered, yielding 5.0 g of gray solid. This precipitate was dissolved in acetonitrile and on cooling gave 4.0 g (81%) of 1,1,2-triphenylisoindoline, mp 181–183°. Further recrystallization from acetonitrile–methanol (1:1) afforded an analytical sample: mp 182–183°; ir (KBr) no OH or NH, 745 (1,2 disubstituted), 730, and 690 cm^{-1} (monosubstituted); nmr ($CDCl_3$) δ 4.95 (s, 1.9, $PhCH_2$), 6.5–7.6 (m, 19.2, aromatic).

Condensation of 4 with Benzaldehyde. Formation of *o*-(*N*-Phenylaminomethyl)diphenylcarbinol (19).—A hexane solution of 6.3 g (0.0595 mol) of benzaldehyde was added to the suspension of **4**, and the mixture was stirred for 10 hr. The milky white suspension was neutralized and worked up as described above. The ether solution of **19** was dried ($MgSO_4$), concentrated, and then distilled under reduced pressure to give 4.2 g (72–75%) of a viscous yellow oil (**19**), bp 205–210–212° (0.06 mm). Repeated efforts to crystallize this oil were successful: ir (neat) 3590 (OH), 3320 cm^{-1} (NH); nmr ($CDCl_3$) 4.0 (s, 1.97, $PhCH_2^-$), 5.86 (s, 1 $>C(O^-)H$).

Acylation of 19 with Acetic Anhydride.[23]—Approximately 2.0 g (0.007 mol) of carbinolamine **19** was placed into a 100-ml erlenmeyer flask, along with 15 ml of acetic anhydride. The resulting green mixture was heated (mild reflux) for 10–15 min, cooled, and then mixed with an equal amount of water. The viscous green oil which formed in cooling was extracted into ether. The combined ether extracts were washed with 30 ml of 10% hydrochloric acid, dried ($MgSO_4$), and then concentrated to a green oil. This residue was dissolved in 15 ml of methanol; cooling this solution with the addition of ice gave a white solid which was collected by filtration. Recrystallization from aqueous methanol afforded 0.7 g (30%) of white crystalline solid mp 131°–132°; ir (KBr) 1750 (-COO-), 1680 cm^{-1} (-CON$^-$-), nmr ($CDCl_3$) δ 1.85 (s, 2.8, $-COCH_3$), 2.0 (s, 2.9, $-COCH_3$), 4.76 (H_A), 5.14 (H_B) (AB q, 1.8, J_{AB} = 14 Hz, $PhCH_AH_B$), 5.9 (s, 0.5, >C-H).

Cyclization of Carbinolamine 19 with 20% Sulfuric Acid. Formation of 1,2-Diphenylisoindoline (22).—Into a 100-ml round-bottomed flask were placed 5.0 g (0.0172 mol) of carbinolamine **19** and 50 ml of 20% sulfuric acid. This mixture was refluxed 2–3 hr, cooled, and then poured into an aqueous sodium hydroxide solution. The resulting basic solution was stirred for 30 min and then an equal volume of ether was added. Stirring was continued until all the solid had dissolved. Then the aqueous portion was separated and washed with 100 ml of ether. The combined ether fractions were dried ($MgSO_4$) and then concentrated. The resulting residue was dissolved in acetonitrile–methanol (1:1); cooling this solution afforded solid product, mp 152–155°. Several recrystallizations from benzene–hexane afforded an analytical sample: ir (KBr) no OH or NH; nmr ($CDCl_3$) δ 4.74 (H_A),* 5.07 (H_B),* 5.82 (H_C)* (J_{AB}* = 13, J_{AC}* = 3, J_{BC}* = 0.5–1.1 Hz, $ArCH_CNC_6H_5CH_AH_BAr$) (the asterisk denotes approximate values).

Condensation of 4 with 9-Fluorenone. Formation of 9-[o-(*N*-Phenylaminomethyl)phenyl-9-fluorenol (20).—An ether solu-

(23) Solid diacylated derivative of carbinolamine **19**.

tion of 6.0 g (0.035 mol) of 9-fluorenone was added to the suspension of **4**, and the mixture was stirred for 1 hr. The yellow-green suspension was neutralized and worked up as described above to give 7.95 g (93–98%) of white solid, mp 154–156°. Recrystallization from benzene–hexane and then absolute EtOH afforded an analytical sample: mp 155–156°; ir (KBr) 3550 (OH), 3385 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.3 (s, 2, $PhCH_2$), 3.6 (broad s, 0.9, OH), 3.9 (s, 1, NH).

Cyclodehydration of 20 with 20% Sulfuric Acid. Formation of Fluorene-9-spiro-1′-phenylisoindoline (23).—Into a 100-ml round-bottomed flask were placed 4.0 g (0.011 mol) of carbinolamine **20** and 60 ml of 20% sulfuric acid. This mixture was refluxed 4 hr, cooled, and then poured into a sodium hydroxide solution. The resulting white suspension was stirred for 30 min and then filtered, yielding 2.52 g (67%) of white solid. This precipitate was dissolved in absolute ethanol, cooled, and filtered, yielding a white solid, mp 174–176°. Addition of ice to the filtrate afforded a second crop of crystals. Further recrystallization from aqueous ethanol afforded an analytical sample: ir (KBr) no OH or NH; nmr ($CDCl_3$) δ 5.18 (s, 1.9, $PhCH_2$), 6.2–7.9 (m, 17, aromatic).

Condensation of 4 with Acetophenone. Formation of 1,1-[o-(*N*-Phenylaminomethyl)diphenyl]methanol (24).—A hexane solution of 3.4 g (0.028 mol) of acetophenone was added to the suspension of **4** precooled in an ice bath for 15 min. After a stirring period of 30–45 min, the yellow-white solution was neutralized and worked up as described above to give 0.9 g (10%) of white solid, mp 139–142°. (Amine **3** was recovered in 65–75%.) Attempts to improve the yield of **24** by condensing lithioamine **4** at −80 were unsuccessful; ir (KBr) 3430 (OH), 3285 cm^{-1} (NH); nmr ($CDCl_3$) δ (1.85 (s, 2.7, $>C(O^-)CH_3$), 3.7 (H_A), 3.9 (H_B) (AB q, 2, $J_{AB_{app}}$ = 12 Hz, $PhCH_2$).

Carbonation of Lithioamine 4. Formation of *o*-(*N*-Phenylaminomethyl)benzoic Acid (25).—To the magnetically stirred yellow-white suspension of lithioamine **4** were added small pieces of carbon dioxide over a 15-min period. The resulting milky white slurry was stirred for 30 min and then poured into 50 ml of 10% hydrochloric acid. The acidic solution was stirred for 5 min, 100 ml of ether was added, and stirring was continued another 30 min. The light-red acid layer was separated from the organic layer. The organic fraction was dried ($MgSO_4$) and then concentrated to give 0.3–0.4 g (8%) of 2-phenylphthalimidine (**26**), mp 157–160°. Recrystallization from absolute methanol afforded a white crystalline solid, mp 159–161°.

The acid layer was made basic with sodium hydroxide pellets; when cool, the basic aqueous solution was stirred with an equal volume of ether for 30 min. The ether layer was separated and then washed with 50 ml of 10% sodium hydroxide. The combined basic fractions were carefully acidified to pH 5 with concentrated hydrochloric acid. Cooling and scratching afforded 3.0 g (61%) of green-white solid which was collected by filtration. The solid acid did not melt but decomposed between 103 and 107° to form the lactam, which melted at 158–161°: ir (KBr) 3020–2780 (broad) (OH), 1680 (>C=O), 1400 and 1252 (OH and C–O), 867 cm^{-1} (OH).

Thermal Cyclization of Amino Acid (25). Formation of 2-Phenylphthalimidine (26).—The solid amino acid **25** was placed in a 250-ml beaker and heated on a hot plate until all the solid had melted. The beaker was cooled and then the solid was dissolved in methanol; the solvent was slowly removed by gentle heating. The resulting solid was again dissolved in methanol, cooled, and filtered, yielding 2.4–2.5 g (90%) of crystalline white solid, mp 160–162°. One recrystallization from absolute methanol gave a white crystalline solid: mp 162–163° (lit.[24] mp 162–163°); ir (KBr) 1690 (five-membered lactam); nmr ($CDCl_3$) δ 4.75 (s, 1.8, $C_6H_5CH_2$–), 6.9–8.3 (m, 9.3, aromatic).

Registry No.—TMEDA, 110-18-9; *n*-butyllithium, 109-72-8; **1**, 103-67-3; **3**, 103-32-2; **6**, 28504-92-9; **7**, 15496-39-6; **7** (dibenzoylated derivative), 28504-94-1; **8**, 28504-95-2; **9**, 28504-96-3; **10**, 28504-97-4; **12**, 28504-98-5; **13**, 28504-99-6; **14**, 28505-00-2; **15**, 28505-01-3; **16**, 28505-02-4; *cis*-**17**, 28505-03-5; *trans*-**17**, 28505-04-6; **18**, 28505-05-7; **19**, 28505-06-8; **19** diacetate, 28505-07-9; **20**, 28519-58-6; **21**, 28607-62-7; **22**, 28519-59-7; **23**, 28519-60-0; **24**, 28519-61-1; **25**, 28519-62-2; **26**, 5388-42-1.

(24) J. R. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965, p 2711.

A Direct Preparation of Amidines. The Reaction of Tetrakis(dimethylamino)titanium with N–H Carboxamides

JAMES D. WILSON,* JANICE S. WAGER, AND HAROLD WEINGARTEN

Monsanto Company, Central Research Department, St. Louis, Missouri 63166

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Tetrakis(dimethylamino)titanium reacts with N-monosubstituted carboxamides to give free trisubstituted amidines. Benzamide is converted to a mixture of benzonitrile and *N*,*N*-dimethylbenzamidine, and 1*H*-2-pyridones yield 2-dimethylaminopyridines. This reaction appears to be the first direct conversion of amides to trisubstituted amidines. Nmr spectral data are presented for the amidines prepared.

Although we know of many reactions which lead to amidinium salts,[1] conversion to their conjugate bases, amidines, cannot always be achieved in good yield.[2] Previous reports from this laboratory have described the reactions of various carboxylic acid derivatives with tetrakis(dimethylamino)titanium (**1**) by which reaction carboxylic anhydrides, *N*,*N*-dialkylamides, and esters are all converted to alkylidene bis(dialkylamines).[5] Thus it was of interest to study the reactions of **1** with a series of N–H amides to see (1) whether carbon and titanium can undergo nitrogen–nitrogen ligand exchange reactions similar to the carbon-bound oxygen for titanium-bound nitrogen exchanges previously observed,[5] and (2) if amidines can be directly prepared this way. We report our results here.

Results and Discussion

The reactions of several N-monosubstituted amides with tetrakis(dimethylamino)titanium were observed; the products and their physical properties are presented in Table I. In general, the reactions appear to follow eq 1 although no quantitative reactions were observed. The conditions employed were generally similar to those previously employed:[5] the reagents were mixed, either

(1) (a) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York, N. Y., 1965, pp 182–194.

(2) This is particularly true for the smaller, aliphatic amidines. Thus Short and his coworkers consistently obtained lower yields of aliphatic than aromatic amidines in their extensive research in the area.[3] Similar results were reported by Pettit and Garson.[4]

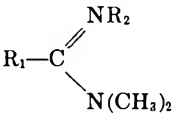
(3) P. Oxley and W. F. Short, *J. Chem. Soc.*, 147 (1946), 382 (1947), and subsequent publications.

(4) G. R. Pettit and L. R. Garson, *Can. J. Chem.*, **43**, 2640 (1965).

(5) H. Weingarten and W. A. White, *J. Amer. Chem. Soc.*, **88**, 850 (1966); H. Weingarten and W. A. White, *J. Org. Chem.*, **31**, 2874 (1966).

TABLE I

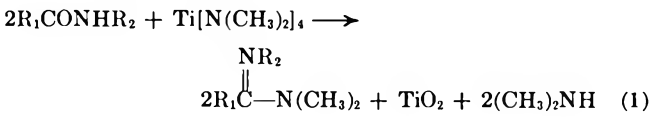
PHYSICAL PROPERTIES OF AMIDINES PREPARED



Product[a] R1	R2	Registry no.	Bp, °C (Torr)	Mol wt[f]	Nmr,[h] τ	% C[n]	% H	% N
H	C_6H_5	1783-25-1	85 (1.0)	148	7.3 s (6 H), 3.0 m (5 H), 2.5 s (1 H)		*j*	
H	*tert*-C_4H_9	23314-06-9	28 (17)	128	8.9 s (9 H), 7.2 s (6 H), 2.7 s (1 H)		128.1305[k] (128.1313)	
CH_3	CH_3	28504-67-8	72 (75)	100	7.1 s (3 H), 7.2 s (6 H), 8.2 s (3 H)	59.95 (60.00)	12.02 (12.00)	28.00 (28.00)
C_6H_5	CH_3	25092-88-0	42 (0.2)	162	2.5 m (5 H), 7.2 s (3 H), 7.3 s (6 H)	73.31 (74.04)	9.34 (8.70)	17.32 (17.27)
tert-C_4H_9	CH_3	28504-69-0	75 (55)	142	7.2 s (3 H), 7.4 s (6 H), 8.9 s (9 H)[i]			
$-(CH_2)_3-$		1003-55-0	80 (30)	112	6.6 t (2 H), 7.2 s (6 H), 7.6 m (4 H)	64.56 (64.25)	10.86 (10.80)	24.32 (24.06)
$-CH_2OCH_2CH_2-$[b]		28504-71-4	125 (35)	128	5.8 s (2 H), 6.6 m (4 H)	55.49 (56.22)	9.43 (9.45)	21.96[l] (21.84)
$-CH{=}CHCH{=}CH-$[c]		5683-33-0	90 (40)	122	1.7 m (1 H), 2.5 m (1 H), 3.3 m (2 H), 6.9 s (6 H)			
$-CH{=}CN{=}C-$[d] (CH_3 CH_3)		5177-09-3	61 (0.8)	139	3.8 s (1 H), 7.0 s (6 H), 7.6 s (3 H), 7.8 s (3 H)			
CH_3	$C(NMe_2){=}CH_2$[e]	28504-74-7	58 (0.55)	*g*	6.3 s (2 H), 7.2 s (12 H), 7.9 s (3 H)			
C_6H_5	H[m]	20548-18-9	115 (0.25)	148	2.7 m (5 H), 7.2 s (6 H)			

[a] In each case the starting material was the amide R_1CONHR_2. [b] Starting material, 3-ketomorpholine. [c] Product, 2-(dimethylamino)pyridine. [d] Product, 4-(dimethylamino)-2,6-dimethylpyrimidine. [e] Starting material, diacetamide. [f] Mass number of parent ions. [g] Parent ion not observed. [h] CD_3CN solution, internal TMS reference. [i] Dioxane solution. [j] Mass and ir spectra compared with those of authentic sample. [k] Molecular weight from high-resolution mass spectrum. [l] Oxygen: 13.44% found; 12.47% calculated. [m] Benzonitrile is also produced in this reaction. See Experimental Section. [n] Calculated values in parentheses.

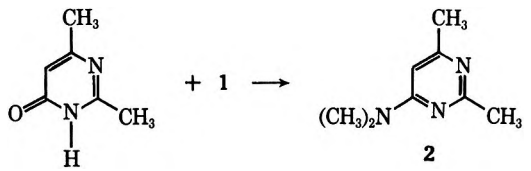
neat or in an unreactive solvent (ether, benzene, THF), and heated if necessary, and the product was recovered by distillation.



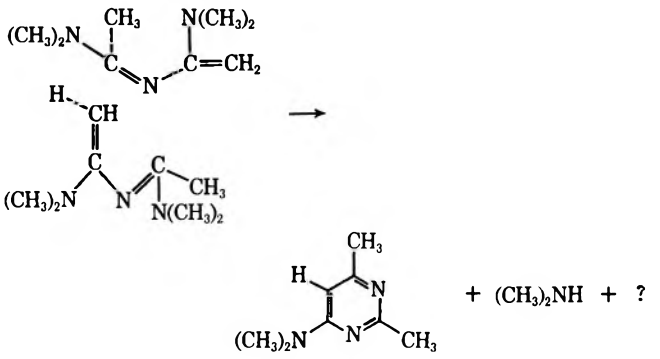
$$2R_1CONHR_2 + Ti[N(CH_3)_2]_4 \longrightarrow 2R_1C(=NR_2)-N(CH_3)_2 + TiO_2 + 2(CH_3)_2NH \quad (1)$$

The only products observed in this work were those derived by amination of the carbonyl function.[6] From this we conclude that, at least in these simple systems, amide ligand exchange occurs much more slowly than amination. This presumably reflects the relatively greater strength of Ti–O than Ti–N bonds.

Three products require further comment. The conversion of 2-pyridone and 2,4-dimethyl-6-pyrimidone into respectively 2-(dimethylamino)pyridine and 4-(dimethylamino)-2,6-dimethylpyrimidine (2) represents a new kind of entry into aminoheterocyclic systems. This reaction should be applicable in most heterocyclic series.



Diacetamide, $(CH_3CO)_2NH$, reacts with 1 to give $CH_3C(NMe_2){=}NC(NMe_3){=}CH_2$ (3) which is formally an amidine but which is perhaps best regarded as an aza derivative of the 1,3-bis(dimethylamino)butadienes.[7] Pyrolysis of 3 at about 100° unexpectedly gives a product identified as 2 by comparison of its mass and nmr spectra with those of the compound prepared from 2,4-dimethyl-6-pyrimidone. This condensation parallels the base-catalyzed cyclotrimerization of acetonitrile to 6-amino-2,4-dimethylpyridimine.[8] The stoichiometry of the pyrolysis requires the disposition of another fragment (or fragments) corresponding to $C_2H_2(NMe_2)_2$ but no evidence was seen for one logical compound of that formula, vinylidenebis(dimethylamine). A sample of 3 was pyrolyzed during introduction into a mass spectrometer, but there was no significant peak at *m/e* 114, which there would have been if any quantity of vinylidenebis(dimethylamine) were present in the pyrolysate.



Benzamide, unsubstituted on nitrogen, reacts with 1 to give a 53% yield of benzonitrile and 26% of *N*,*N*-

(6) Except, of course, the benzonitrile from benzamide (see below).

(7) H. Weingarten and M. G. Miles, *J. Org. Chem.*, **33**, 1506 (1968); H. Weingarten, M. G. Miles, S. R. Byrn, and C. F. Hobbs, *J. Amer. Chem. Soc.*, **89**, 5974 (1967).

(8) R. Schwarze, *J. Prakt. Chem.*, **42**, 1 (1890).

dimethylbenzamidine,[9] indicating that competition exists between dehydration and substitution in this reaction. Although this was not studied, it seems likely that conditions could be chosen so as to achieve good yields of either amidine or nitrile.

N,N'-Dimethyloxamide reacts with **1** to give an insoluble, involatile product which strongly resembles brick dust. This may be a high molecular weight coordination polymer,[10] but it has not been characterized.

Experimental Section

Chemicals and solvents used in this work were obtained from Fisher Scientific or Aldrich Chemical Corp. unless otherwise noted. Solvents were the driest commercially available and not further treated. Tetrakis(dimethylamino)titanium was obtained from Alfa Inorganics. Nmr spectra were determined using a Varian A-60, in CD_3CN solvent with TMS reference. Mass spectra were obtained on a CEC-104 spectrometer and ir spectra on a Beckman IR-4. Boiling points are uncorrected.

***N,N*-Dimethyl-*N'*-butylformamidine.**—To a stirred solution of 8.08 g (0.08 mol) of *tert*-butylformamide in 200 ml of dry THF was added dropwise 10.75 g (0.048 mol) of tetrakis(dimethylamino)titanium. The reaction was allowed to reflux for 48 hr. The titanium dioxide precipitate was then removed by filtration and washed with pentane. The solvent was removed from the combined filtrate and washings under reduced pressure and the liquid residue distilled at reduced pressure to give 5.0 g (51%) of a colorless liquid, bp 28° (17 Torr). The structure was confirmed by nmr and low and high resolution mass spectrometry. (Table I. The high resolution mass spectrum was obtained on a CEC-110 instrument.)

The following compounds were obtained from reaction virtually identical with that described above; only differences from it and additional relevant data will be presented here.

***N,N*-Dimethyl-*N'*-phenylformamidine.**—From 12.1 g (0.10 mol) of formanilide and 11.2 g (0.05 mol) of **1**, 7.90 g (72%) of the product was obtained after 3 days reaction at 25°. Its structure was proved by comparison of its ir, nmr, and mass spectra with those of an authentic sample from Frinton Laboratories.

***N,N,N'*-Trimethylacetamidine.**—From 7.3 g (0.10 mol) of *N*-methylacetamide and 12.5 g (0.056 mol) of **1**, 3.14 g (31%) of the product was obtained. It was characterized from the data given in Table I.

***N,N,N'*-Trimethylbenzamidine.**—Reaction of 13.5 g (0.10 mol) of *N*-methylbenzamide with 11.2 g (0.05 mol) of **1** for 18 hr at 25° yielded 6.30 g (90%) of a colorless liquid characterized as above.

***N,N,N'*-Trimethylpivalamidine.**—The reaction of 5.75 g (0.05 mol) of *N*-methylpivalamide (Frinton Laboratories) with 6.75 g (0.03 mol) of **1** for 48 hr at reflux in dioxane solvent gave 1.0 g (14%) of a colorless liquid characterized by its mass and nmr spectra.

***N,N*-Dimethyl-2-(1-pyrrolinyl)amine.**—The reaction of 8.95 g (0.04 mol) of **1** with 6.35 g (0.075 mol) of 2-pyrrolidone, neat, for 24 hr at 100°, yielded 3.72 g (37%) of a colorless liquid characterized by elemental and spectral analyses.

3-Dimethylamino-5,6-dihydrooxazine.—From 5.05 g (0.05 mol) of 3-ketomorpholine and 8.96 g (0.04 mol) of **1**, reaction for 48 hr, neat, at 80°, 2.60 g (40%) of product was obtained. It was characterized as above.

2-(Dimethylamino)pyridine.—From a reaction of 4.75 g (0.05 mol) of 2-pyridone with 6.75 g (0.03 mol) of **1** for 3 days at reflux (in THF solution), 1.0 g (16%) of a colorless product was obtained which was characterized as above. The picrate (from ethanol) exhibited mp 182–183° (lit.[11] 181–182°).

4-(Dimethylamino)-2,6-dimethylpyrimidine.—The reaction of 2.48 g (0.02 mol) of 2,4-dimethyl-6-hydroxypyrimidine with 2.30 g (0.012 mol) of **1**, for 3 days at reflux, gave 0.50 g (17%) of a colorless liquid, characterized as above. The picrate (from ethanol) exhibited mp 177–179° (lit.[12] 177°).

Reaction of Benzamide with 1.—To a solution of 6.5 g (0.05 mol) of benzamide in 25 ml of dry benzene was added, dropwise with stirring, 5.60 g (0.025 mol) of **1**. The mixture was refluxed for 4 hr, after which time it was colorless. The precipitated TiO_2 was removed by filtration, and the benzene solvent was removed from the filtrate by distillation at atmospheric pressure. The remaining yellow liquid was distilled under reduced pressure, giving fractions boiling at 90° (2 Torr) (2.37 g) and 115° (25 Torr) (2.30 g). The first was identified as benzonitrile by comparison of the glpc retention times (on a column made up of OV-17 on high-performance Chromosorb G) and infrared spectra of it and an authentic sample. The second was characterized by its mass and nmr spectra. From the nmr spectrum it appeared that the sample contained about 15% benzonitrile; the phenyl hydrogen adsorptions of the two compounds are separated well enough for approximate integral areas of the two peaks to be measured. From these data the yields of the two compounds were benzonitrile (53%) and *N,N*-dimethylbenzamide (26%).

Reaction of Diacetamide with 1.—To a stirred solution of 4.04 g (0.04 mol) of diacetamide in 30 ml of acetonitrile was added 9.0 g (0.042 mol) of **1**, dropwise with stirring, giving a two-phase reaction mixture (**1** is only slightly soluble in CH_3CN). This mixture was allowed to reflux for 2 days, the precipitated TiO_2 was then filtered off, and the acetonitrile removed from the filtrate by reduced-pressure evaporation. The yellow liquid residue was distilled under reduced pressure at 58–83° (1.0 Torr) giving a mixture of two compounds which were identified as 4-(dimethylamino)-2,6-dimethylpyrimidine and 2,4-bis(dimethylamino)-3-aza-1,3-pentadiene by their mass and nmr spectra. The pyrimidine was confirmed by independent synthesis (above); the azapentadiene spectra were then deduced by substraction of the peaks arising from the pyrimidine.

Registry No.—Tetrakis(dimethylamino)titanium, 7229-79-0.

(9) Glpc results imply that the conversion of benzamide was not complete under these conditions.

(10) Polymeric coordination complexes of N,N'-disubstituted dithiooxamides with various transition metals are well known. See F. G. A. Stone and W. A. Graham, "Inorganic Polymers," Academic Press, New York, N. Y., 1962.

(11) L. Pentimalli, *Gazz. Chim. Ital.*, **94**, 458 (1964).

(12) D. J. Brown, B. T. England, and J. M. Lyall, *J. Chem. Soc. C*, 226 (1966).

Electrophilic Halogenation of 8-Quinolinol and Its Copper(II) Chelate[1]

HERMAN GERSHON,* MAYNARD W. MCNEIL, AND STEPHEN G. SCHULMAN

Boyce Thompson Institute for Plant Research, Yonkers, New York 10701, and College of Pharmacy, J. Hillis Miller Health Center, University of Florida, Gainesville, Florida 32601

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Electrophilic halogenation of 8-quinolinol and its copper(II) chelate with elemental halogen and *N*-halosuccinimide was studied. Under acidic conditions, substitution at the 5 position of 8-quinolinol was favored, during chlorination and bromination, and, in basic media, the 7 position was favored. Iodination was characterized by the reverse orientation and may take place by a different mechanism. Orientation of substituents in the monohalogenation of 8-quinolinol is influenced by its prototropic form, the halogenating agent, and the solvent employed. MO calculations consistent with the experimental results are reported.

There has been considerable interest in 8-quinolinol and its derivatives, since the reports of Hahn[2] and Berg[3] established the value of those compounds as precipitants of metal ions. Further interest has been elicited by the studies of Zentmyer,[4] Albert, *et al.*,[5] and Gershon, *et al.*,[6] who related the mechanism of fungitoxicity of the 8-quinolinols, in part, to chelation of metals.

In a comprehensive review of the literature to 1956, Hollingshead[7] concluded that on reaction of 8-quinolinol with excess elemental halogen only 5,7-dihalogeno-8-quinolinols resulted. On using equimolar quantities of reactants, substitution occurred in the 5 position, but the product was always contaminated with some 5,7-disubstituted derivative. More recent work on the halogenation of 8-quinolinol has yielded a variety of results.[8-14]

Of further interest were studies of the effect of chelation on halogenation of 8-quinolinol. Maguire and Jones[15] concluded, as a result of dihalogenation reactions on metal chelates of this ligand with elemental chlorine, bromine, and iodine, that coordination does not alter the reactive positions of 8-quinolinol toward electrophilic reagents. On the basis of competitive bromination of metal chelates of 8-quinolinol in the presence of free ligand with elemental bromine, Hix and Jones[16] stated that the rate of bromination of chelates was about 35 times greater than that of the free ligand. In attempting to generalize these concepts to electrophilic reactions of bis(8-quinolinolato)copper(II), Chawla and Jones[17] reported that benzoylation, sulfonation, nitration, thiocyanation, mercuration, and condensation with formaldehyde can be readily effected on the chelate. Iodination was achieved in poor yield and acetylation failed. The halogenation of metal chelates of 8-quinolinol with *N*-halosuccinimido was reported by Prasad, *et al.*,[18] and reinvestigated by Gershon, *et al.*[14,19] These results allowed for the following conclusions. Chelation increases the rate of halogenation and does not change the reactive positions in electrophilic substitution. This is in agreement with the work of Hix and Jones[16] and Maguire and Jones.[15] Chelation does affect orientation of substituents in electrophilic substitution with *N*-halosuccinimide.[19]

In view of the diversity of results obtained from the variety of halogenation methods, a systematic study of the halogenation of 8-quinolinol and its copper(II) bischelate using elemental chlorine, bromine, and iodine was desired. Halogenations were carried out in chloroform at ambient temperatures for 3 hr and the ratios of halogen to substrate were 1:1, 2:1, and 3:1. The rationale for this approach and the identification and quantitation of the products were previously discussed.[14,19] The results of the reactions are compiled in Table I. On chlorination of 8-quinolinol and its copper(II) chelate with elemental chlorine, it was again confirmed that the rate of chlorination is greater for the chelate than for the ligand.[16] This is apparent from the greater uptake of chlorine by the chelate as compared with the ligand during the experimental time. The outstanding difference observed in this chlorination reaction is that the ligand yielded measurable quantities of 7-chloro-8-quinolinol, whereas the chelate afforded only insignificant yields of this isomer.

The products of bromination of 8-quinolinol and its copper(II) chelate with 1 equiv of bromine per equivalent of quinolinol were not greatly different. Doubling the ratio of bromine to 8-quinolinol resulted in the formation of only 5,7-dibromo-8-quinolinol. With respect to the chelate, 2 and 3 equiv of bromine, at ambient temperatures, caused the formation of tarry products which were unsuitable for analysis. This bromination was successfully carried out by Hix and Jones[16] at 0–5°.

The action of 1 equiv of iodine on 1 equiv of 8-quinolinol resulted in the formation of 5-iodo-, 7-iodo-, and 5,7-diiodo-8-quinolinol with most of the iodine entering the 5 position. On doubling the ratio of iodine, all three products were formed in greater yield, but the results of 3 equiv of iodine were essentially the same as

(1) This work was supported in part by the U. S. Public Health Service, Grant No. AI-05808.

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(6) H. Gershon, S. G. Schulman, and D. Olney, *Contrib. Boyce Thompson Inst.*, **24**, 167 (1969).

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(8) H. Fiedler, *J. Prakt. Chem.*, **13**, 86 (1961).

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(10) Olin Mathieson Chemical Corp., French Patent 1,372,414 (1964); *Chem. Abstr.*, **62**, 13130 (1965).

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(15) K. D. Maguire and M. M. Jones, *J. Amer. Chem. Soc.*, **84**, 2316 (1962).

(16) J. E. Hix, Jr., and M. M. Jones, *J. Inorg. Nucl. Chem.*, **26**, 781 (1964).

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Table I

Action of Elemental Halogen on 8-Quinolinol and Its Copper(II) Complex in Chloroform at Ambient Temperatures

Halogenating agent	Molecular ratio or halogen to substrate	Products, % (as free ligands)[a]							
		8-Quinolinol				Bis(8-quinolinolato)copper(II)			
		Ox[b]	5-ClOx	7-ClOx	5,7-Cl_2Ox	Ox	5-ClOx	7-ClOx	5,7-Cl_2Ox
Chlorine	1	46	20	5	30	40	18	Tr[c]	42
	2	2	43	2	54	2	9	Tr	89
	3	0	0	0	100	Tr	3	Tr	97
		Ox	5-BrOx	7-BrOx	5,7-Br_2Ox	Ox	5-BrOx	7-BrOx	5,7-Br_2Ox
Bromine	1	48	4	1	47	41	14	Tr	45
	2	Tr	Tr	0	99	...[d]			
	3	0	0	0	100				
		Ox	5-IOx	7-IOx	5,7-I_2Ox	Ox	5-IOx	7-IOx	5,7-I_2Ox
Iodine	1	65	30	3	1	...[e]			
	2	47	39	8	6				
	3	43	39	9	9				

[a] All results are the average of three runs with an average deviation of ±10%. [b] Ox = 8-quinolinol. [c] Tr = trace (<1%). [d] Two and three equivalents of bromine caused the formation of tarry products which were unsuitable for analysis. [e] This reaction was complicated by the apparent reduction of Cu(II) to Cu(I) with accompanying release of unchelated 8-quinolinol.

those from 2 equiv. The iodination of bis(8-quinolinolato)copper(II) with elemental iodine was not examined becuase this reaction was complicated by the apparent reduction of copper(II) to copper(I) with accompanying release of 8-quinolinol. This will be the subject of an additional study. It appears that this reduction was not recognized by Chawla and Jones[17] who treated the copper(II) chelate of 8-quinolinol with a little more than 2 equiv of iodine. They reported that a gummy product was obtained which on decomposition yielded 6.6% of 5,7-diiodo-7-quinolinol and 6.5% of a second product which, on the basis of melting point, was claimed to be 5-iodo-8-quinolinol.

A comparison of the halogenation of 8-quinolinol and its copper(II) chelate using *N*-halosuccinimide[14,19] and elemental halogen shows that the rate of chlorination of 8-quinolinol with elemental chlorine is greater than that with *N*-chlorosuecinimide (NCS). On monohalogenation, chlorine favored the formation of 5-chloro- over 7-chloro-8-quinolinol, while with NCS the reverse was true. The same held for the copper(II) chelate except that with NCS, 5- and 7-chloro-8-quinolinols formed in about equal yields. The rates of bromination of the ligand and the chelate with elemental bromine and *N*-bromosuccinimide (NBS) were rapid and indistinguishable in all cases, under the conditions studied; however, of the monosubstitution products of the reaction of 8-quinolinol and its copper(II) chelate with bromine, the 5-bromo formed in preference to the 7-bromo analog, whereas with NBS the yield of 7-bromo exceeded that of 5-bromo-8-quinolinol, on bromination of the ligand. Only 5-bromo-8-quinolinol was obtained from the chelate. The rate of iodination of 8-quinolinol with *N*-iodosuccinimide (NIS) was much greater than that with iodine, and, in both cases, the orientation was primarily in the 5 position. With respect to the chelate, reaction with NIS resulted in the formation of primarily the 7 isomer.[14,19] Data with elemental iodine were not obtained, as was previously explained.

It was of further interest to examine the effect of the solvent and of the prototropic form on the orientation of substituents in the halogenation of 8-quinolinol by elemental halogen and by *N*-halosuccinimide. For this study, 8-quinolinol was treated with chlorine, bromine, iodine, NCS, NBS, and NIS on a 1:1 equiv basis. The following solvents ranging in decreasing acidity were employed: 93% sulfuric acid, glacial acetic acid, pyridine, diethylamine, sodium hydroxide equivalent to the free halogen and the quinolinol, and excess 10% sodium hydroxide. In the case of iodine, iodination was also attempted with iodine dissolved in excess 47% hydriodic acid. The results are summarized in Table II. Equivalent studies on the bischelate with copper(II) were not undertaken because of the instability of the chelates in the extreme acidic and basic media. Chawla and Jones[17] reported the sulfonation of bis(8-quinolinolato)copper(II) in concentrated sulfuric acid, whereas 8-quinolinol could not be sulfonated under these conditions. Of interest was the fact that the 5-sulfonic acid was obtained as the free ligand. In view of the stability data of Albert[20] who showed that the β_2 values for the copper(II) chelates with 8-quinolinol and 8-quinolinol-5-sulfonic acid were 23.4 and 23.1, respectively, it appears unlikely that bis(8-quinolinolato)copper(II) was sulfonated since it would not have been stable in concentrated sulfuric acid as was the bis copper(II) chelate of the sulfonic acid. The sulfonation reaction in the presence of copper(II) may have been due to a catalytic action of the metal. Similarly, that the copper(II) chelate of 8-quinolinol was nitrated in 40% nitric acid is also subject to question because it is not likely that the complex would have been stable in such concentrated acid. Therefore, any conclusions drawn from these experiments regarding electrophilic substitution of metal chelates of ligand should be suspect. A study on the stability of bis(5,7-dichloro-8-quinolinolato)copper(II) in acid solution by Gershon, *et al.*,[21] showed that below pH 1.0 no chelate existed.

It can be seen from the data of Table II that on monohalogenation of 8-quinolinol with chlorine, NCS, bromine, or NBS in strongly acidic media the incoming halogen atom was oriented primarily to the 5 position. In strongly basic media, the halogen atom favored the 7 position. Halogenation in acidic environments which were less acidic than 93% sulfuric acid allowed for the formation of mixtures of 5- and 7-halogeno-8-quinolinols; however, the 5 isomer predominated. In basic media

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TABLE II

EFFECTS OF SOLVENTS ON ELECTROPHILIC HALOGENATION OF 8-QUINOLINOL[a]

	Products, %							
	N-Chlorosuccinimide				Chlorine			
Halogenating medium	Ox[b]	5-ClOx	7-ClOx	5,7-Cl_2Ox	Ox	5-ClOx	7-ClOx	5,7-Cl_2Ox
H_2SO_4, 93%	1	99	0	Tr[c]	Tr	96	3	1
Acetic acid, glacial	24	37	24	15	39	18	7	36
Pyridine	42	10	32	16	67	9	9	15
Diethylamine	100	0	0	0	93	1	6	0
NaOH, 3 equiv					38	5	52	5
NaOH, 10% (excess)	29	6	60	5	39	3	51	7
	N-Bromosuccinimide				Bromine			
	Ox	5-BrOx	7-BrOx	5,7-Br_2Ox	Ox	5-BrOx	7-BrOx	5,7-Br_2Ox
H_2SO_4, 93%	Tr	99	0	Tr	0	99	0	Tr
Acetic acid, glacial	28	33	13	26	34	35	0	31
Pyridine	17	16	45	22	41	13	24	22
Diethylamine	21	0	78	Tr	13	3	80	4
NaOH, 3 equiv					84	3	4	9
NaOH, 10% (excess)	74	0	16	10	89	0	8	3
	N-Iodosuccinimide				Iodine			
	Ox	5-IOx	7-IOx	5,7-I_2Ox	Ox	5-IOx	7-IOx	5,7-I_2Ox
H_2SO_4, 93%	49	1	49	1	100	0	0	0
Acetic acid, glacial	18	17	39	26	84	12	3	1
Pyridine	22	34	18	26	14	59	5	12
Diethylamine	1	88	4	7	47	32	4	17
NaOH, 3 equiv					99	Tr	Tr	0
NaOH, 10% (excess)	58	11	4	27	93	2	3	2
HI, 47%					100	0	0	0

[a] All results are the average of three runs with an average deviation of ±10%. [b] Ox = 8-quinolinol. [c] Tr = trace (<1%).

which were less basic than 10% sodium hydroxide, mixtures of 5- and 7-substituted 8-quinolinols were formed, but 7 substitution was favored. This is consistent with the observation of Pearson, *et al.*,[13] who reported that on bromination of phenols the presence of hydrogen bromide caused substitution to take place in the para position and, conversely, in the absence of hydrogen bromide substitution favored the ortho position.

The course of iodination seemed to be different from that of chlorination or bromination. Iodination of 8-quinolinol with NIS in strongly acidic media caused the iodo substituent to enter the 7 position, and, in strongly basic media, orientation favored the 5 position. Elemental iodine was ineffective as an iodinating agent in strong acid as well as in strong base. In the weaker bases, diethylamine and pyridine, monoiodination by both agents resulted in the formation of greater yields of 5-iodo-8-quinolinol than the 7 isomer. In acetic acid, the products formed from the different iodinatng agents did not follow the same pattern in orientation.

It thus appears that orientation of substituents in the monohalogenation of 8-quinolinol is affected by the prototropic form of the substrate, the halogenating agent, and the solvent employed.

In view of the foregoing results, the generalization of Hollingshead,[7] that on monohalogenation of 8-quinolinol only the 5-substituted product is formed, is to be questioned. The present data are also in contradiction to the report of Mychajlyszyn[11] who claimed that 5-chloro-8-quinolinol along with 5,7-dichloro-8-quinolinol was formed by chlorination of 8-quinolinol with sodium hypochlorite in sodium hydroxide. The methods of halogenation in sulfuric acid of Sukhina[9] and Aristov and Kostina[12] were herein confirmed.

In attempting to explain the reactivity of 8-quinolinol and its metal chelates toward both electrophilic and nucleophilic reagents, Burton and Davis[22] carried out Hückel LCAO calculations on the cationic, neutral, and anionic forms of the ligand. These calculations have been quoted[23] and used as the basis for further calculations[24] and in essence they state that, for electrophilic reagents, the electrophilic localization energies indicate that the preferred position for attack is the 5 position regardless of the prototropic form of the substrate. These calculations are inconsistent with the results of the present work, and it would be in order to reexamine them.

The simple Hückel calculations[22] fail to account for interelectronic repulsion in the total energy of the molecular species. A modification of the Hückel approach by Bancroft and Howe[25] allows for its refinement by including interelectronic repulsions.

In the present work, charge densities for the anion, neutral, and cation species derived from 8-quinolinol were evaluated from an eigenvalue routine on an IBM 7072 digital computer using the parameters suggested by Burton and Davis[22] for estimating the oxygen and nitrogen Coulomb integrals and the carbon–oxygen and carbon–nitrogen resonance integrals for all prototropic species concerned. In addition, π-electron charge densities were calculated for the O doubly protonated species derived from 8-quinolinol (see structure a). The rapid increase observed in absorptivity and change in shape of the absorption spectra of 8-quinolinol in solution with increasing concentrations of sulfuric acid, but below that which effects sulfonation, suggested that such a species may exist in these solutions. The Cou-

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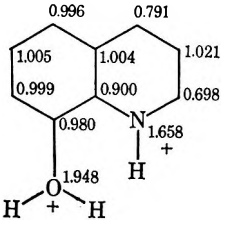
Table III

Electrophilic Localization Energies (ΔE_π),[a] Interelectronic Repulsion Correction Terms (ΔE_r), and Corrected Electrophilic Localization Energies ($\Delta E_\pi' = \Delta E_\pi + \Delta E_r$). Corresponding to Electrophilic Substitution at the 5 and 7 Positions of the Anion, Neutral Species, Cation, and Doubly Charged Cation Derived from 8-Quinolinol

	ΔE_π		ΔE_r		$\Delta E_\pi'$	
Prototropic form	5	7	5	7	5	7
Anion	2.35×10^{-11}	2.41×10^{-11}	4.02×10^{-11}	3.73×10^{-11}	6.37×10^{-11}	6.14×10^{-11}
Neutral species	2.53×10^{-11}	2.66×10^{-11}	3.85×10^{-11}	3.80×10^{-11}	6.38×10^{-11}	6.56×10^{-11}
Cation	3.40×10^{-11}	3.58×10^{-11}	3.95×10^{-11}	4.10×10^{-11}	7.35×10^{-11}	7.68×10^{-11}
Doubly charged cation	3.02×10^{-11}	3.28×10^{-11}	4.22×10^{-11}	5.04×10^{-11}	7.24×10^{-11}	8.32×10^{-11}

[a] ΔE_π, ΔE_r, and $\Delta E_\pi'$ are expressed in ergs per molecule.

lomb integral for doubly protonated oxygen was taken to be $\alpha_c + 2.25\beta_{cc}$, where α_c is the carbon Coulomb integral and β_{cc} is the carbon–carbon resonance integral,



a

while the resonance integral for the C–CH_2^+ bond was taken to be $0.8\beta_{cc}$. These values were selected by noting the changes in the Coulomb and resonance integrals in the treatment of Burton and Davis,[22] upon going from the anion to the neutral species and applying these changes to the singly protonated species.

The interelectronic repulsion terms were calculated using the carbon–carbon bond length of 1.40 Å as the length of all bonds in the π system which included the carbon–oxygen and carbon–nitrogen bonds. Errors for those approximations are expected to be very small. In order to convert the localization energies calculated from the simple Hückel theory from units of β_{cc} to the same units as those of the repulsion terms, it was necessary to evaluate β_{cc}. This was accomplished by relating the energy of the lowest π–π^* transition in units of β_{cc} to the experimentally determined quantity evaluated from the long wavelength absorption maximum of each prototropic species. The electrophilic localization energies calculated from the simple Hückel treatment, the repulsion terms, and the corrected localization energies for substitution at the 5 and 7 positions of the anion, neutral species, cation, and doubly charged cation, respectively, derived from 8-quinolinol are presented in Table III.

The values of $\Delta E_\pi'$ in Table III indicate that electrophilic halogenation should occur at the 5 position as the preferred site in all prototropic species derived from 8-quinolinol except for the anion. Electrophilic substitution should occur preferentially in the 7 position in the anion. These calculated results are in good agreement with the experimental data for chlorination and bromination of 8-quinolinol but not for iodination. This would indicate that the mechanism of iodination may be different from that of chlorination and bromination.

Experimental Section[26]

Halogenation of 8-Quinolinol and Its Bis Copper(II) Complex with Elemental Halogen in Chloroform.—To 10 ml of chloroform containing 5 mmol of elemental halogen (Cl_2, Br_2, or I_2) was added 1, 2, or 3 mequiv of 8-quinolinol or its Cu(II) complex. The mixture was stirred on a magnetic stirrer for 3 hr, after which the free ligands and the chelates were assayed according to ref 14 and 19.

Halogenation of 8-Quinolinol in Different Solvents with Elemental Halogen and *N*-Halosuccinimides.—For halogenations carried out in 93% H_2SO_4, acetic acid, pyridine, diethylamine, NaOH, and HI, the procedure was similar to that described above for the free ligands, except for chlorination with Cl_2 in 93% H_2SO_4. For this, the required amount of Cl_2 was condensed in a small calibrated test tube cooled by a Dry Ice–acetone bath. It was then poured into a solution of 8-quinolinol in 93% (w/w) H_2SO_4 in a citrate of magnesia bottle and stirred magnetically. The assay was carried out as above.

Registry No.—8-Quinolinol, 148-24-3; 8-quinolinol copper(II) chelate, 10380-28-6.

(26) Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector to which was attached a Varian Aerograph Model 20 recorder. The column and conditions employed for the gas chromatographic separation of the chloro- and bromo-8-quinolinols were described previously[14] as were the column and conditions for the iodo-8-quinolinols.[19]

Mass Spectroscopy of Organosilicon Compounds. Examples of Interaction of the Silyl Center with Remote Phenyl Groups

WILLIAM P. WEBER* AND ALVIN K. WILLARD

Department of Chemistry, University of Southern California, University Park, Los Angeles, California 90007

HEINZ G. BOETTGER

Jet Propulsion Laboratory, California Institute of Technology, Pasadena, California 91103

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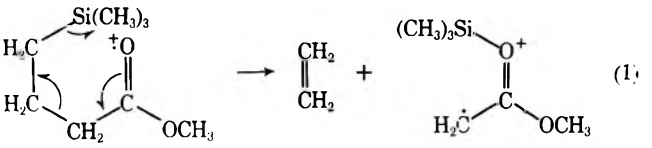
The mass spectra of 1-(trimethylsilyl)-3-phenylpropane and β-(trimethylsilyl)styrene have been studied in detail. The mass spectral rearrangements observed are shown to occur by interaction of the silyl center and the phenyl ring.

Mass spectroscopy is a particularly powerful analytical method of structure determination. The occurrence of molecular rearrangements of ions, often with concurrent fragmentation, in the mass spectrometer complicates the determination of the original structure. Certainly such rearrangements must be recognized if fragment ions are to provide useful structural data. Two major types of rearrangements involving silyl centers have been observed. The first involves the direct transfer of an intact trimethylsilyl group from one part of the ion to another with concurrent fragmentation in a manner similar to certain types of hydrogen migrations frequently observed in mass spectroscopy, such as the McLafferty rearrangement.[1-4] The second involves interaction of a siliconium ion center, formed by loss of a methyl group from silicon in the parent ion, with distant electron-rich centers in the molecule.[4-7] These rearrangements are important for the understanding of the mass spectra of organosilicon compounds. The fact that related rearrangements involving the silyl center sometimes occur in volatile trimethylsilyl ether derivatives makes these rearrangements of more general interest. This is true because these derivatives have been a frequent choice for the separation and structure determination of nonvolatile materials by a combination of gas chromatography and mass spectroscopy.[6-10] We propose to discuss two examples of the interaction of a silyl center with a remote phenyl group in mass spectroscopy.

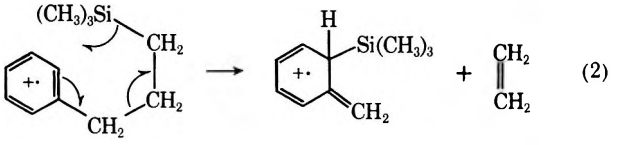
Several examples of the apparent migration of a trimethylsilyl group from an ether oxygen to a positively charged carbonyl oxygen functionality in the mass spectrometer have been reported.[1,2] More recently the probable transfer of a trimethylsilyl group from the γ-carbon of an alkyl chain to a positively charged carbonyl oxygen in a silyl–McLafferty-type rearrangement has been observed (eq 1).[4]



(1)

We would now like to report a new example of the high migratory aptitude of a trimethylsilyl group in which this group is transferred from a saturated carbon atom to an unsaturated carbon atom in the mass spectrometer.

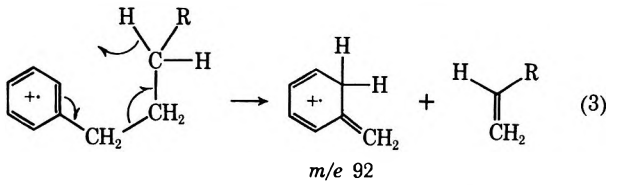
The peak at mass 164 in the mass spectrum of 1-(trimethylsilyl)-3-phenylpropane probably results from migration of the trimethylsilyl group from the terminal γ-carbon of the alkyl chain to the positively charged phenyl ring with simultaneous loss of ethylene (eq 2) (see Tables I–III for substantiating data). A meta-



(2)

stable peak at mass 140 [calculated $m/e = (164)^2/192 = 140.1$] provides evidence in support of this rearrangement. The mass spectra of both 1-(trimethylsilyl)-1,1-dideuterio-3-phenylpropane and 1-(trimethylsilyl)-3-deuterio-3-phenylpropane were examined and found to support the proposed rearrangement (see Tables I and II).

This rearrangement is similar to the transfer of a hydrogen from the γ-carbon of an alkylbenzene to the phenyl ring with concurrent β fragmentation.[11] This leads to formation of the mass 92 ion and a neutral olefin molecule. It has been shown that the γ-hydrogen is transferred to the ortho position of the phenyl ring by the observation that the rearrangement does not occur if both ortho positions are blocked (2,4,6-trimethyl-1-octadecylbenzene) (eq 3).[12] While the



m/e 92

(3)

position on the phenyl ring to which the trimethylsilyl group is transferred has not been determined by our

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TABLE I

MASS SPECTRUM OF 1-(TRIMETHYLSILYL)-3-PHENYLPROPANE AND RELATED DEUTERIUM-LABELED COMPOUNDS AT 70 eV

Mass, m/e	Rel intensity $C_6H_5(CH_2)_3Si(CH_3)_3$	Rel intensity $C_6H_5(CH_2)_2CD_2Si(CH_3)_3$	Rel intensity $C_6H_5CHD(CH_2)_2Si(CH_3)_3$
72	7.1	5.2	8.3
73	100.0	100.0	100.0
74	39.2	38.8	42.3
75	33.0	32.8	18.9
76	1.8	2.2	2.8
77	3.6	10.1	5.6
78	1.8	6.6	5.6
79		4.5	2.8
80		1.0	
85	2.7		5.6
86		1.2	
87	1.8	1.2	
88		3.2	
89	1.8	5.4	
90		3.6	
91	22.3	24.2	11.5
92	1.8	16.1	27.8
93		7.2	3.3
94		10.8	
101	80.3		74.5
102	8.9	2.0	8.3
103	4.5	79.6	3.9
104		8.9	2.8
105	1.8	6.6	3.3
106		1.3	
107		1.4	
115	3.6	1.1	3.9
116		3.2	6.7
117	8.9	4.7	8.3
118	2.7	3.5	8.3
119	1.8	12.0	3.3
120		5.1	2.8
121	2.7	3.4	3.5
129	9.8		
130			
131	1.8		
132			
133	1.8	1.4	
134			
135	10.7	5.9	13.9
136	1.8	1.4	1.7
144	2.7		
145	1.8		
146	3.6	1.4	
159	1.8		
160			
161	2.7		
162		1.4	2.8
163		3.0	
164	34.8	21.6	6.7
165	5.4	3.5	31.7
166	1.8		4.4
167	0.9		1.7
177	66.0		8.9
178	11.6		61.2
179	2.7	48.1	9.5
180		5.7	2.9
181		1.3	
192	7.1		2.1
193	1.8		9.5
194	0.9	2.8	1.1
195		0.4	0.6
196		0.06	

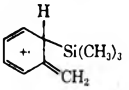
TABLE II

MASS SPECTRUM OF 1-(TRIMETHYLSILYL)-3-PHENYLPROPANE AND RELATED DEUTERIUM-LABELED COMPOUNDS AT 20 eV

Mass m/e	Rel intensity $C_6H_5(CH_2)_3Si(CH_3)_3$	Rel intensity $C_6H_5(CH_2)_2CD_2Si(CH_3)_3$	Rel intensity $C_6H_5CHD(CH_2)_2Si(CH_3)_3$
73	100.0	83.3	65.7
74	8.1	16.1	5.7
75	5.4	6.8	2.1
76		3.1	
101	75.6	1.5	100.0
102	8.1	2.8	10.0
103	2.7	100.0	2.9
104		16.7	
105		5.6	
106		0.6	
161		0.6	
162		3.1	
163		0.9	
164	35.1	80.9	11.4
165	5.4	15.4	43.6
166	1.4	3.7	7.1
167		0.6	1.4
176		0.6	
177	41.9	3.1	11.4
178	6.8	1.8	41.4
179	1.4	72.8	7.9
180		14.2	1.4
181		3.7	
182		0.6	
192	5.4	0.4	1.7
193	1.4	0.3	6.3
194		7.4	0.7
195		1.5	
196		0.6	

TABLE III

HIGH-RESOLUTION MASS SPECTRAL DATA AT 70 eV
$C_6H_5CH_2CH_2CH_2Si(CH_3)_3$

Elemental composition	Calcd mass	Obsd mass	Possible structure of ion
$C_{11}H_{17}Si$	177.1099	177.1097	$C_6H_5(CH_2)_3\overset{+}{S}i(CH_3)_2$
$C_{10}H_{16}Si$	164.1021	164.1054	
$C_8H_{11}Si$	135.0630	135.0645	$C_6H_5\overset{+}{S}i(CH_3)_2$
$C_6H_{13}Si$	101.0786	101.0783	$(CH_3)_3SiCH_2\overset{+}{C}H_2$
C_7H_7	91.0548	91.0542	Tropylium ion
C_3H_9Si	73.0473	73.0473	$(CH_3)_3\overset{+}{S}i$

results, we favor a six-membered ring transition state with transfer of the trimethylsilyl group to the ortho position of the phenyl ring by analogy to the alkylbenzene behavior. This migration of a trimethylsilyl group from a saturated carbon of an alkyl chain to the unsaturated phenyl ring is only an important process when the trimethylsilyl group is on the γ-carbon and hence when a six-membered ring transition state is possible. In the mass spectrum of 1-(trimethylsilyl)-4-phenylbutane, no ion at mass 164 was observed. The usual transfer of a hydrogen from the γ-carbon of the alkyl side chain to the phenyl ring does occur in this compound, leading to a significant ion at mass 92. (see Tables IV and V for substantiating data).

Several additional ions in the mass spectrum of 1-(trimethylsilyl)-3-phenylpropane deserve comment.

TABLE IV

MASS SPECTRUM OF 1-(TRIMETHYLSILYL)-4-PHENYLBUTANE AT 70 EV

$C_6H_5(CH_2)_4Si(CH_3)_3$

Mass	Rel intensity	Mass	Rel intensity
71		119	2.2
72	3.1	120	
73	100.0	121	1.9
74	8.7		
75	4.1	129	2.8
76		130	
77	3.1	131	2.2
78	1.5	132	18.7
79	1.2	133	2.2
		134	
82	1.5	135	3.1
83	12.5		
84	1.2	189	4.7
		190	
87	5.6	191	34.4
		192	6.6
91	18.7	193	1.6
92	5.9		
		206	7.2
97	2.2	207	1.6
		208	
103	1.6		
104	3.4		
105	1.6		
115	1.2		

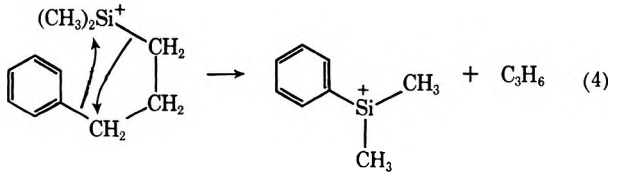
TABLE V

HIGH-RESOLUTION MASS SPECTRAL DATA AT 70 EV

$C_6H_5CH_2CH_2CH_2CH_2Si(CH_3)_3$

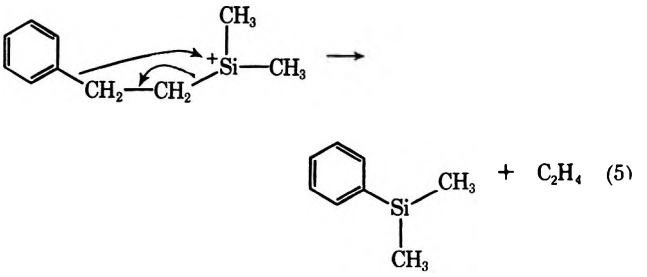
Elemental composition	Calcd mass	Obsd mass	Possible structure of ion
$C_{13}H_{22}Si$	206.1491	206.1486	Parent
$C_{12}H_{19}Si$	191.1256	191.1227	$C_6H_5(CH_2)_4\overset{+}{S}i(CH_3)_2$
$C_8H_{11}Si$	135.0630	135.0638	$C_6H_5\overset{+}{S}i(CH_3)_2$
$C_{10}H_{12}$	132.0939	132.0927	
C_7H_7	91.0548	91.0552	Tropylium ion
C_3H_7Si	73.0473	73.0468	$(CH_3)_3Si^+$

The ion at mass 177 results from loss of a methyl group from the parent ion. Fragmentation at such a highly branched center producing this ion is a favored process. Rearrangement of this ion with migration of the electron-rich phenyl group to the siliconium ion center with simultaneous loss of C_3H_6, possibly as cyclopropane, leads to formation of the dimethylphenylsiliconium ion at mass 135. The observation of a metastable ion at mass 103 [calculated $m/e = (135)^2/177 = 103$] provides evidence in support of this rearrangement (eq 4).



(4)

The mass spectra of both 1-(trimethylsilyl)-1,1-dideuterio-3-phenylpropane and 1-(trimethylsilyl)-3-deuterio-3-phenylpropane support this proposed rearrangement (see Tables I, II, and III). A similar rearrangement in the case of 1-(trimethylsilyl)-2-phenylethane has been observed (eq 5) (see Table VI).[13,14]



(5)

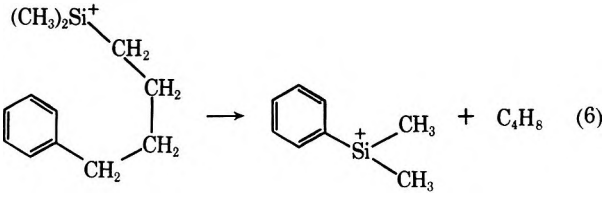
TABLE VI

HIGH-RESOLUTION MASS SPECTRAL DATA AT 70 EV

$C_6H_5CH_2CH_2Si(CH_3)_3$

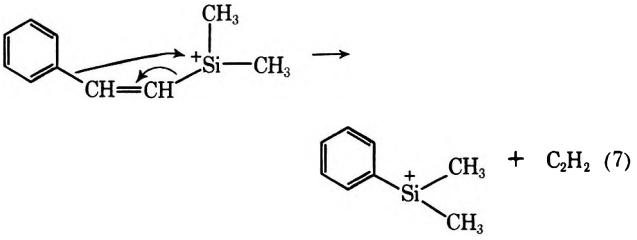
Elemental composition	Calcd mass	Obsd mass	Possible structure of ion
$C_{11}H_{18}Si$	178.1178	178.1184	Parent
$C_{10}H_{15}Si$	163.0943	163.0934	$C_6H_5CH_2CH_2\overset{+}{S}i(CH_3)_2$
$C_8H_{11}Si$	135.0630	135.0633	$C_6H_5\overset{+}{S}i(CH_3)_2$
C_3H_9Si	73.04735	73.0462	$(CH_3)_3Si^+$

Similarly, in the mass spectrum of 1-(trimethylsilyl)-4-phenylbutane a rearrangement of the parent − 15 ion with loss of C_4H_8 leads to the dimethylphenylsiliconium ion at mass 135. It should be noted that this is the only ion in the mass spectrum of 1-(trimethylsilyl)-4-phenylbutane which arises by interaction of the remote phenyl group and the silyl center (eq 6).



(6)

An analogous rearrangement is found in the case of β-(trimethylsilyl)styrene in which acetylene is eliminated as the neutral fragment in the rearrangement of the P − 15 ion to the dimethylphenylsiliconium ion (eq 7) (see Tables VII–IX for substantiating data).



(7)

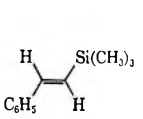
However, in this case loss of acetylene is not so important as is loss of methane from the P − 15 ion. A metastable ion at mass 130.9 [calculated, $(145)^2/161 = 130.6$] provides evidence in support of this pathway. A tempting possibility was the formation of an aromatic (2-π electron) substituted silacyclopropenium cation by

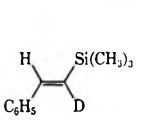
(13) T. H. Kinstle, P. J. Ihrig, and E. J. Goettert, *J. Amer. Chem. Soc.*, **92**, 1780 (1970).

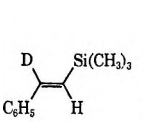
(14) W. P. Weber, R. A. Felix, and A. K. Willard, *Tetrahedron Lett.*, 907 (1970).

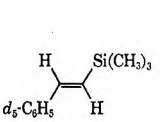
TABLE VII

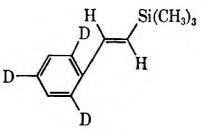
MASS SPECTRUM OF β-(TRIMETHYLSILYL)STYRENE AND RELATED DEUTERIUM-LABELED COMPOUNDS AT 70 eV


A


B

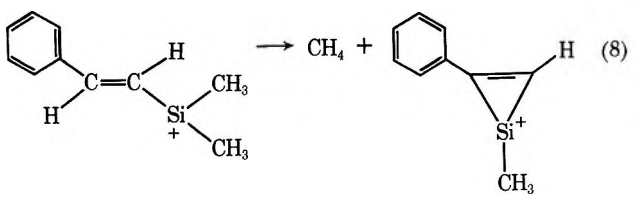

C


D


E

Mass, m/e	A	B	C	D	E	Mass, m/e	A	B	C	D	E
71	1.9					128	1.7				
72	1.3	1.9				129	4.7	2.2	1.5		
73	12.8	20.3	5.5	4.9	6.1	130	2.1	1.6	1.0		
74	3.4	4.8	1.4			131	6.9	4.8	2.8		
75	2.4	2.7			0.6	132	1.4	4.8	3.7		0.7
76	3.3	3.8	1.4			133	10.0	8.6	5.5		1.0
77	7.6	9.7	2.8			134	1.7	7.5	6.4	0.7	1.9
78	3.4	6.8	2.1			135	37.0	56.5	38.5	0.5	2.1
79	3.4	4.3	1.6	0.5	0.9	136	5.6	9.7	8.0	1.2	4.7
80		1.1		0.5	1.0	137	1.9	2.4	2.0	2.0	6.2
81	2.4	4.8	1.8	0.5		138				3.2	31.5
82				2.4	2.0	139				3.8	3.4
83	2.1	2.1				140				33.6	0.9
89	2.1	1.6				141	1.9			3.6	
90		1.2				142	5.0			0.2	
91	4.9	4.8	1.8			143	5.0	2.7	2.0		
92	1.3	3.2	1.6			144	1.5	3.2	3.2		
93	3.4	4.1	1.8			145	85.7	34.9	18.3		0.7
94	1.1	1.4			0.7	146	13.9	76.3	68.3		2.9
95	1.3	1.1		0.6		147	4.9	11.8	10.6	1.2	23.9
96				1.6		148	1.1	3.8	3.2	2.5	32.8
102	2.2	2.7	1.0			149	1.7			33.8	5.2
103	3.4	7.5	2.5			150				13.9	0.8
104	2.1	4.4	1.6			151				1.9	2.1
105	12.6	17.7	8.7		1.1	157	1.4				
106	2.1	4.8	2.5		1.1	158	2.1				
107	4.3	5.4	2.7	1.1	3.1	159	11.3		4.1		
108				0.8	3.6	160	2.9	8.0	8.4		
109	1.9			2.6		161	100.0	35.5	18.3		2.1
110				3.5	0.6	162	16.1	100.0	100.0		7.5
115	6.9	5.6	2.3			163	5.1	16.9	17.2	2.3	17.8
116	2.1	6.6	3.7			164		4.3	4.8	4.8	100.0
117	4.1	5.1	2.2		0.7	165				9.0	15.4
118	1.7	5.4	2.3		1.3	166				100.0	4.4
119	5.6	6.6	3.7	1.2		167				14.8	
120	1.4	3.8	2.3	1.0	0.8	168				3.1	
121	6.9	7.0	4.8	0.5	0.9	175	1.7				
122	1.3	4.8	2.3	1.6	0.6	176	28.9	10.2	4.8		
123			0.5	1.4	0.6	177	6.0	30.0	28.4		
124					3.5	178	2.1	5.7	5.0		4.2
125						179		1.3	1.4		28.5
126						180				1.6	4.0
127						181				27.8	0.8
						182				3.7	
						183					

loss of the α-hydrogen and a methyl group from silicon (eq 8).


(8)

However, the mass spectra of 1-phenyl-1-deuterio-2-(trimethylsilyl)ethylene, 1-phenyl-2-deuterio-2-(trimethylsilyl)ethylene, 1-(2′,4′,6′-trideuteriophenyl)-2-(trimethylsilyl)ethylene, and, finally, 1-pentadeuteriophenyl-2-(trimethylsilyl)ethylene conclusively ruled out this possibility. In all of these four cases deuterium was completely retained in the P − 15 ion. However, the subsequent loss of methane from this ion is a complicated process. Evidence from the labeled compounds indicates that it involves loss of CH_3 from the siliconium ion center and one hydrogen of the styryl portion of the molecule. However, the hydrogen lost does not come from any specific site in the styryl portion of the molecule. Rather, the mass spectra clearly demonstrate that all seven hydrogens of the styryl portion extensively scramble prior to loss of one together

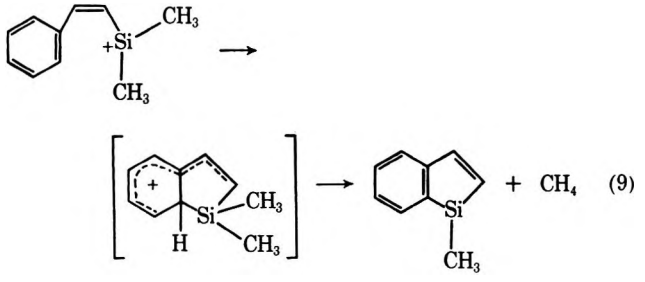
TABLE VIII

MASS SPECTRUM OF β-(TRIMETHYLSILYL)STYRENE AND RELATED DEUTERIUM-LABELED COMPOUNDS AT 20 EV[a]

Mass, m/e	A	B	C	D	E
133	1.3	1.8			
134		1.8	0.5		
135	0.3	9.2	1.0		
136		1.8			
137					
138					0.6
145	3.8	10.0	1.5		
146	0.6	22.0	6.0		
147		3.5	1.0		1.3
148		1.4			2.4
149				1.4	
159		2.1			
160		2.1	1.0		
161	100.0	3.2	16.9		
162	15.9	100.0	100.0		0.6
163	4.4	16.3	17.2		16.6
164		4.2	4.5		100.0
165					15.3
166				8.0	4.1
167				100.0	
168				15.2	
169				2.7	
176	77.5	17.0	11.6		
177	13.3	51.1	74.2		
178	3.8	9.2	12.6		11.6
179		2.5	3.5		72.7
180				5.1	11.4
181				73.7	2.6
182				11.1	
183				1.6	

[a] See structures for A–E in Table VII.

with the methyl group from silicon as methane. A possible mechanism for this scrambling process involves initial electrophilic attack by the siliconium ion center on the phenyl ring. Scrambling of the seven hydrogens of the styryl systems occurs by rapid proton shifts in this intermediate, prior to loss of methane, possibly to form an indenylsiliconium ion (eq 9) (see Tables VII and VIII).



The mass spectrum of 1-(trimethylsilyl)-2-phenylacetylene has only two major ions, the parent at mass 174 and the P − 15 due to loss of a methyl group from the quaternary silyl center, at mass 159. A doubly charged ion at mass = 159/2 = 79.5 is significant. In this case the linear nature of the acetylenic linkage, as well as the impossibility of losing a stable neutral species, probably prevents interaction between the silyl center and the phenyl ring (see Tables X and XI).

TABLE IX

HIGH-RESOLUTION MASS SPECTRAL DATA AT 70 EV

$C_6H_5CH{=}CHSi(CH_3)_3$

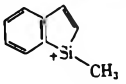
Elemental composition	Calcd mass	Obsd mass	Possible structure of ion
$C_{11}H_{16}Si$	176.1021	176.1021	Parent
$C_{10}H_{13}Si$	161.07865	161.0798	$C_6H_5CH{=}\overset{+}{C}HSi(CH_3)_2$
$C_{10}H_{11}Si$	159.0630	159.0632	$C_6H_5C{\equiv}\overset{+}{C}Si(CH_3)_2$
C_9H_9Si	145.04735	145.0472	
$C_8H_{11}Si$	135.0630	135.0620	$C_6H_5\overset{+}{S}i(CH_3)_2$
C_8H_8	104.0626	104.0618	
C_8H_7	103.0548	103.0548	
$C_5H_{13}Si$	101.07865	101.0781	$(CH_3)_3SiCH_2\overset{+}{C}H_2$
C_7H_7	91.05477	91.0555	Tropylium ion
C_6H_5	77.0391	77.0415	$C_6H_5^+$
C_3H_9Si	73.04735	73.0475	$(CH_3)_3Si^+$

TABLE X

MASS SPECTRUM OF 1-(TRIMETHYLSILYL)PHENYLACETYLENE AT 70 EV

$C_6H_5C{\equiv}CSi(CH_3)_3$

Mass	Rel intensity	Mass	Rel intensity
75	1.4	128	1.4
76	1.0	129	12.8
77	7.1	130	1.8
78	1.4	131	7.8
79	2.8	132	
[79.5]	5.7	133	1.4
80	1.0		
		142	1.4
89	2.8	143	5.3
90	1.4	144	1.4
91	3.5	145	2.1
93	1.4	159	100.0
		160	14.9
101	1.8	161	4.3
102	3.5		
103	6.3	174	17.7
104	1.0	175	2.8
105	12.8	176	0.7
106	1.6		
107	2.6		
115	8.5		
116	2.1		
117	3.9		
118			
119	1.4		

TABLE XI

HIGH-RESOLUTION MASS SPECTRAL DATA AT 70 EV

$C_6H_5C{\equiv}CSi(CH_3)_3$

Elemental composition	Calcd mass	Obsd mass	Possible structure of ion
$C_{11}H_{14}Si$	174.08647	174.0861	Parent
$C_{10}H_{11}Si$	159.0630	159.0677	$C_6H_5C{\equiv}\overset{+}{C}Si(CH_3)_2$

Obviously, the interaction of a silyl center with a phenyl group plays a dominant role in the mass spectra of the compounds discussed.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. All compounds described were purified for mass spectral study by preparative gas chromatography on a 10 ft × 0.25 in. SE-30 column. Ir spectra were determined as neat liquids on a Perkin-Elmer 337 ir spectrometer. Nmr spectra were run on a Varian A-60 nmr spectrometer using 10% solutions in carbon tetrachloride. Either chloroform or methylene chloride was used as internal standard.

Conditions used in determining low-resolution mass spectra on the Hitachi RMU-6E instrument were as follows: source temperature, 200°; all-glass inlet temperature, 200°; ionizing voltage, 70 and 20 eV; filament emission, 70 μA; and target current, 50 μA. Comparisons were made between unlabeled compounds at 20 eV and labeled compounds at 20 eV under identical conditions.

Conditions used in determining high-resolution spectra on the AEI MS-902 instrument were as follows. The exact mass determination of the composition of important ions was carried out at a resolution of at least 10,000. Exact mass was determined by peak matching with peaks of known mass of perfluorokerosene. The ionizing voltage was 70 eV; filament emission was 480 μA; and source temperature was 150°.

1-(Trimethylsilyl)-3-phenylpropane[15] was prepared by a coupling reaction between the Grignard reagent formed from 1-bromo-3-phenylpropane (Aldrich) and trimethylchlorosilane (Alfa Inorganics). The reaction was carried out in a three-necked, 200-ml, round-bottomed flask equipped with a reflux condenser, a pressure equalizing addition funnel, a nitrogen inlet, and a magnetic stirring bar. The flask was charged with 1.5 g (0.06 g-atom) of magnesium turnings (Mallinckrodt). The apparatus was flamed to dryness under a stream of nitrogen. Trimethylchlorosilane (7.6 g, 0.07 mol) in 100 ml of tetrahydrofuran was added to the flask, and 10.0 g (0.05 mol) of 1-bromo-3-phenylpropane was added dropwise. The reaction started immediately. The bromide was added at such a rate that a gentle reflux was maintained, and the reaction mixture was stirred for an additional hour. The reaction was then hydrolyzed by the addition of 50 ml of water. Ether (100 ml) was added and the organic and aqueous layers were separated. The organic layer was washed twice with 50-ml portions of water, dried over anhydrous magnesium sulfate, and filtered; the solvent was removed by evaporation under reduced pressure. The residue was distilled through a 15-cm vacuum-jacketed Vigreux column yielding 8.5 g (89% yield) of 1-(trimethylsilyl)-3-phenylpropane, bp 112° (35 mm). The physical properties of the compound thus prepared were in complete accord with literature values.

1,1-Dideuterio-1-(trimethylsilyl)-3-phenylpropane (98% d_2) was prepared by coupling the Grignard reagent prepared from 1-bromo-1,1-dideuterio-3-phenylpropane with trimethylchlorosilane in THF. The necessary bromide was synthesized as follows. 3-Phenylpropionic acid (Eastman) was converted to the corresponding methyl ester by treatment with 100 ml of methanolic HCl. The product, methyl 3-phenylpropionate, was purified by distillation, bp 236° (760 mm). 1,1-Dideuterio-3-phenylpropan-1-ol was prepared by reduction of this methyl ester with lithium aluminum deuteride (98% deuterium) in ether solvent in 95% yield. This alcohol was converted to the corresponding tosylate by reaction with recrystallized (ligroin) *p*-toluenesulfonyl chloride in ether in the presence of 1.1 equiv of pyridine. The desired bromide was prepared from the tosylate by reaction with anhydrous lithium bromide in acetone. This bromide contained 98% d_2 by 20-eV mass spectral analysis.

1-Deuterio-1-phenyl-3-(trimethylsilyl)propane (78% d_1).—1-Bromo-1-phenyl-3-(trimethylsilyl)propane was treated with 4 equiv of lithium aluminum deuteride in ether solution for 18 hr. A 50% yield of 1-deuterio-1-phenyl-3-(trimethylsilyl)propane was obtained (78% d_1). The required bromide was prepared from 1-phenyl-3-(trimethylsilyl)propane by treatment with 1.1 equiv of *N*-bromosuccinimide in carbon tetrachloride solution. The reaction was initiated by irradiation with a sun lamp. Succinimide was removed by suction filtration. The solvent was removed by evaporation under reduced pressure. The residue was distilled under vacuum to give a 71% yield of 1-bromo-1-phenyl-3-(trimethylsilyl)propane, bp 60° (0.2 mm). 1-Bromo-1-phenyl-3-(trimethylsilyl)propane was characterized by its nmr spectrum (CH_2Cl_2, δ 5.35, as internal standard): δ 0.14 (9 H), 0.71 t (2 H), 2.26 m (2 H), 4.96 t (1 H), 7.46 s (5 H).

1-Phenyl-4-(trimethylsilyl)butane[15] was prepared by coupling the Grignard reagent formed from 1-bromo-4-phenylbutane with trimethylchlorosilane as above in 91% yield. The required bromide was synthesized from 4-phenylbutyric acid (Aldrich). The acid was converted to methyl 4-phenylbutyrate [bp 90° (0.3 mm)] by treatment with methanolic HCl. Reduction of the methyl ester with lithium aluminum hydride in ether gave 4-phenyl-1-butanol (yield 90%). The alcohol was converted to the tosylate by treatment with recrystallized *p*-toluenesulfonyl chloride in ether, in the presence of 1.1 equiv of pyridine. Displacement of the tosylate by lithium bromide in acetone solution gave 1-bromo-4-phenylbutane in 90% yield.

β-(Trimethylsilyl)styrene[16] was prepared by coupling the Grignard reagent prepared from β-bromostyrene (Eastman) with trimethylchlorosilane. The reaction was carried out as described above. The yield of product, bp 81° (3 mm), was 64%.

1-Phenyl-1-deuterio-2-(trimethylsilyl)ethylene.—α-Deuteriobenzaldehyde was prepared by reaction of *tert*-butyl isocyanide[17] and phenyllithium, followed by quenching with D_2O (40% yield).[18] A Perkin condensation between α-deuteriobenzaldehyde and malonic acid (Eastman) employing α-picoline as base gave β-deuteriocinnamic acid (50% yield).[19] Treatment of β-deuteriocinnamic acid with bromine in chloroform gave the expected dibromocinnamic acid. This was converted to α-deuterio-β-bromostyrene by refluxing the dibromocinnamic acid in aqueous base (40% yield).[20] The product contained 86% d_1. Coupling of the Grignard reagent prepared from α-deuterio-β-bromostyrene with trimethylchlorosilane yielded (89%) the desired product which contained 86% d_1. The per cent deuterium content was determined by mass spectrometry.

1-Phenyl-2-deuterio-2-(trimethylsilyl)ethylene.—A Perkin condensation between benzaldehyde and perdeuteriomalonic acid (Merck) using α-picoline as base yielded α-deuteriocinnamic acid in 55% yield.[19] This was converted to β-deuterio-β-bromostyrene as above in 25% overall yield.[20] The product contained 78% deuterium. Coupling of the Grignard reagent prepared from β-deuterio-β-bromostyrene with trimethylcholorosilane yielded the desired product containing 74% deuterium in 70% yield. The per cent deuterium content was determined by mass spectrometry.

2-(Trimethylsilyl)phenylacetylene.[16]—Phenylacetylene (Aldrich) was treated with 1.1 equiv of butyllithium in hexane solution in the presence of 1.1 equiv of *N,N,N′,N′*-tetramethylethylenediamine. The anion which formed almost immediately was quenched with trimethylchlorosilane. The desired product was obtained in 93% yield, bp 110° (25 mm).

1-Pentadeuteriophenyl-2-(trimethylsilyl)ethylene.—To perdeuteriobenzene (99% d_6) (Merck) in the presence of 1.5 equiv of aluminum chloride in *sym*-tetrachloroethane solvent (purified by treatment with concentrated sulfuric acid) was added 1.5 equiv of acetyl chloride at 0°. The reaction was then heated at 60° for 2 hr. An 85% yield of pentadeuterioacetophenone was obtained. Reaction of pentadeuterioacetophenone with phosphorus pentachloride converted it to the corresponding 1,1-dichloro-1-phenyl-d_5-ethane. This was treated with sodium amide in liquid ammonia to yield phenyl-d_5-acetylene in 20% overall yield.[21] Treatment of phenyl-d_5-acetylene in the presence of *N,N,N′,N′*-tetramethylethylenediamine with *n*-butyllithium followed by quenching of the anion with trimethylchlorosilane gave 1-(trimethylsilyl)-2-phenyl-d_5-acetylene in 85% yield. Hydrogenation of 1-(trimethylsilyl)-2-phenyl-d_5-acetylene over Raney nickel catalyst in methanol at 1-atm pressure yielded a mixture of unreacted acetylene, the desired ethylene, and the completely hydrogenated ethane. These were separated on a 10 ft × 0.25 in. TCEP column. The desired 1-(trimethylsilyl)-2-phenyl-d_5-ethylene was obtained in 40% yield. This compound was found to be 94% d_5.

1-(2′,4′,6′-Trideuteriophenyl)-2-(trimethylsilyl)ethylene was prepared from bromobenzene-2,4,6-d_3. Bromobenzene-2,4,6-d_3

(15) M. C. Musolf and J. L. Speier, *J. Org. Chem.*, **29**, 2519 (1964).

(16) D. Seyferth, L. G. Vaughan, and R. Suzuki, *J. Organometal. Chem.*, **1**, 437 (1964).

(17) I. Ugi, U. Fetzer, U. Ehdzer, H. Knupfer, and K. Offermann, *Angew. Chem. Int. Ed. Engl.*, **4**, 472 (1965).

(18) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).

(19) J. R. Johnson, *Org. React.*, **1**, 248 (1942).

(20) R. Fittig and F. Binder, *Justus Liebigs Ann. Chem.*, **195**, 141 (1879).

(21) J. Casanova, Jr., M. Geisel, and R. N. Morris, *Org. Prep. Proced.*, **1**, 81 (1969).

was prepared by the method of Scarbourgh.[22] Its purity by mass spectroscopy was 86% d_3 and 14% d_2. The corresponding hexadeuterated diphenylmercurial was prepared by the reaction of the Grignard reagent made from the bromide with anhydrous mercuric chloride. Reaction of the deuterated diphenylmercury with a slight excess of trimethylvinylsilane in methanol solvent in the presence of a catalytic amount of anhydrous palladium chloride and a stoichiometric amount of cupric chloride to affect the reoxidation of the palladium overnight at room temperature led to a 10% yield of the desired compound. This procedure is basically that of Heck, applied to trimethylvinylsilane.[23,24] Surprisingly only the trans olefin was obtained. The compound was purified for mass spectral study by gc on a 3 m × 0.25 in. SE-30 column at 160°. The deuterated β-(trimthylsilyl)styrene obtained had the following isotopic purity: 86% d_3 and 14% d_2 by mass spectroscopy.

(22) J. M. Scarbourgh, U. S. Atomic Energy Commission, NAA-SR-2144 (1957); *Chem. Abstr.*, **52**, 9042d (1958).
(23) R. F. Heck, *J. Amer. Chem. Soc.*, **90**, 5538 (1968).
(24) R. Asano, I. Moritani, Y. Fujiwara, and S. Teranishi, *Chem. Commun.*, 1293 (1970).

Registry No.—1-(Trimethylsilyl)-3-phenylpropane, 775-24-6; 1,1-dideuterio-1-(trimethylsilyl)-3-phenylpropane, 28901-25-9; 1-deuterio-1-phenyl-3-(trimethylsilyl)propane, 28901-26-0; 1-phenyl-4-(trimethylsilyl)-butane, 777-82-2; 1-(trimethylsilyl)-2-phenylethane, 772-64-5; β-(trimethylsilyl)styrene, 18001-47-3; 1-phenyl-2-deuterio-2-(trimethylsilyl)ethylene, 28901-30-6; 1-phenyl-1-deuterio-2-(trimethylsilyl)ethylene, 28901-31-7; 1-pentadeuteriophenyl-2-(trimethylsilyl)-ethylene, 28901-32-8; 1-(2′,4′,6′-trideuteriophenyl)-2-(trimethylsilyl)ethylene, 28901-33-9; 2-(trimethylsilyl)-phenylacetylene, 2170-06-1; 1-bromo-1-phenyl-3-(trimethylsilyl)propane, 28841-13-6.

Acknowledgments.—We wish to acknowledge a National Science Foundation grant for purchase of the Hitachi RMU-6 mass spectrometer. This research was partially supported by the Caltech President's Fund and NASA Contract NAS 7-100.

The Reaction of 1,1-Dimethyl-2,5-diphenyl-1-silacyclopentadiene with Diphenylacetylene, 2,3-Dimethyl-1,3-butadiene, and Benzyne[1]

R. MARUCA

Hughes Laboratory of Chemistry, Miami University, Oxford, Ohio 45056

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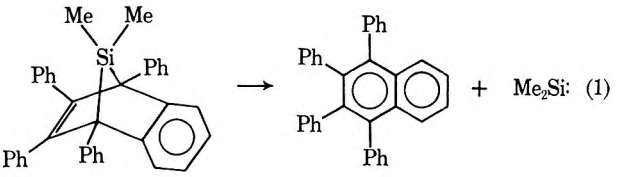
Diphenylacetylene reacts with 1,1-dimethyl-2,5-diphenyl-1-silacyclopentadiene (**4**) to give an isolable 1:1 adduct. Upon pyrolysis in a sealed tube, the adduct not only undergoes dimethylsilylene elimination as has been reported for 7-silanorbornadienes but also disassociates to reactants. When heated under high vacuum or when placed in solution, the adduct again disassociates to reactants. The title silacyclopentadiene reacts with 2,3-dimethyl-1,3-butadiene to give 1,8-diphenyl-3,4,9,9-tetramethyl-9-silabicyclo[4.3.0]nona-3,7-diene (**6**). In this reaction silacyclopentadiene **4** reacts as the dienophile and butadiene as the diene.

Recently, considerable work has been reported on the generation and reaction of several analogs of carbenes.[2-6] As a follow-up of some of this work, an investigation of the reaction of organosilylenes, $R_2Si:$, with a number of compounds was undertaken. This is not only an effort to help characterize these reactive intermediates but is also an effort to prepare compounds which have eluded preparation by other means.

There appears in the literature three distinctly different ways of generating organosilylenes.[2] The first reported was the reaction of an active metal with a dihalodiorganosilane. The other two methods involve the pyrolysis of either a peralkylated polysilane[2] or methoxypolysilanes[5] or the pyrolysis of a 7-silanorbornadiene.[3] The last method has been adopted for this study because it appears to give the silylene intermediate employing the least drastic conditions and also has the least reactive by-products being formed. This last consideration is very important as the coreactants under consideration in the above mentioned investigation are quite reactive with a number of compounds.

Rather than use 2:3-benzo-7,7-dimethyl-1,4,5,6-tetraphenyl-7-silanorbornadiene (**1**)[3] or 7,7-dimethyl-1,2,3,4,5-pentaphenyl-7-silanorbornadiene (**2**)[3] as the precursor to dimethylsilylene (eq 1 and 2), the decision



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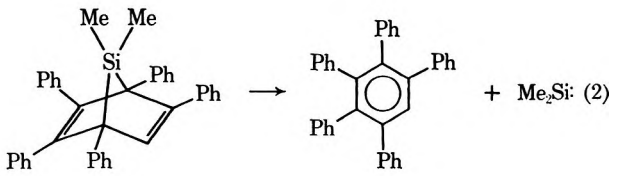
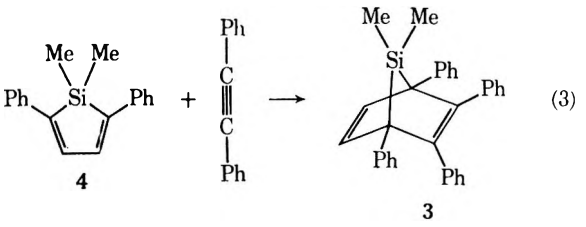


2

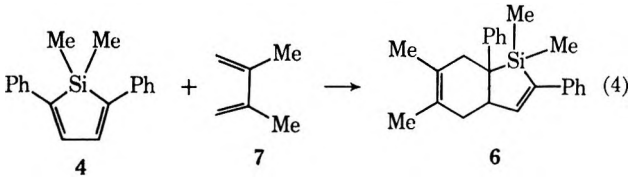
was made to prepare yet another one of these compounds to aid in determining the generality of this method of generation of silylenes as well as to try to obtain a 7-silanorbornadiene which is less stable toward dimethylsilylene elimination than **1** and **2**. The 7-silanorbornadienes are prepared by the Diels–Alder reaction of a silacyclopentadiene with an acetylene. For this investigation it was decided to try to prepare 7,7-dimethyl-1,2,3,4-tetraphenyl-7-silanorbornadiene (**3**) by the reaction (eq 3) of 1,1-dimethyl-2,5-diphenyl-1-

(1) Presented in part at the 2nd Central Regional Meeting of the American Chemical Society, Columbus, Ohio, June 4, 1970.
(2) O. M. Nefedov and M. N. Manakov, *Angew. Chem. Int. Ed. Engl.*, **5**, 1021 (1966).
(3) H. Gilman, S. G. Cottis, and W. H. Atwell, *J. Amer. Chem. Soc.*, **86**, 1596 (1964).
(4) M. E. Vol'pin, *J. Organometal. Chem.*, **8**, 87 (1967).
(5) W. H. Atwell and D. R. Weyenberg, *J. Amer. Chem. Soc.*, **90**, 3438 (1968).
(6) P. L. Timms, *Endeavour*, **27**, 133 (1968).



4 3 (3)

silacyclopentadiene (**4**)[7] with diphenylacetylene (tolan). When silacyclopentadiene **4** was reacted with tolan, a good yield of a 1:1 adduct was obtained as a yellow solid. However, this adduct (**5**) not only eliminates dimethylsilylene as well as any 7-silanorbornadiene reported but also undergoes a disassociation reaction. The acetylenic product from the disassociation is reactive with the coreactants of interest to us, thus eliminating **5** from consideration as a precursor for organosilylenes in this study. Besides the preparation and reactions of the 1:1 adduct, the reaction of silacyclopentadiene **4** with other unsaturated compounds was investigated and the results of these reactions are discussed. In particular, 1,8-diphenyl-3,4,9,9-tetramethyl-9-silabicyclo[4.3.0]nona-3,7-diene (**6**) is formed by the reaction of **4** as a dienophile with 2,3-dimethyl-1,3-butadiene (**7**) as the diene (eq 4).



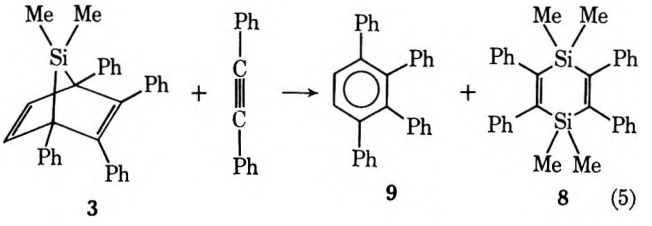
4 7 6 (4)

Results and Discussion

That the reaction of 1,1-dimethyl-2,5-diphenylsilacyclopentadiene with tolan gives a product with a 1:1 stoichiometry has been shown in many ways. All the physical data given for this product are exactly reproducible when determined on samples prepared under different conditions. Using the procedure given in the Experimental Section, preparations were carried out where the molar ratio of silacyclopentadiene to tolan was varied from about 1.5 to 0.5. The same product was received when this reaction was carried out in diglyme solution at 168° or in THF at 68° or when purification was accomplished by recrystallization from petroleum ether (bp 60–90°) hexane or by repeated recrystallization from either of these solvents. The elemental analyses are also in complete agreement with a 1:1 molar ratio of reactants in the product. The real question to be answered, then, concerns the exact nature of the product. That is, is the product a 1:1 solid state complex of some sort or is it a compound having the structure of 7-silanorbornadiene **3**?

The infrared spectrum and melting point of the above 1:1 adduct were determined on solid samples and both are consistent with those expected for a compound or a stable adduct. However, all the rest of the physical data, which were determined on samples of the material in solution or in the gas phase, do not necessarily support this conclusion. In particular, the observed molecular weight is almost exactly half that expected for a stable 1:1 adduct. This is good evidence that there are twice as many species in solution as expected; yet, when the solvent is removed, adduct **5** is recovered unchanged. This and, indeed, all the rest of the physical data taken on solutions are identical with those expected for a 1:1 molar mixture of silacyclopentadiene **4** and tolan, indicating that **5** is a 1:1 solid state complex which dissociates in solution.

A look at some of the chemical reactions of this 1:1 adduct does shed some additional light on its nature. The copyrolysis of it with tolan gives the products expected for 7-silanorbornadiene **3** (eq 5) by analogy to

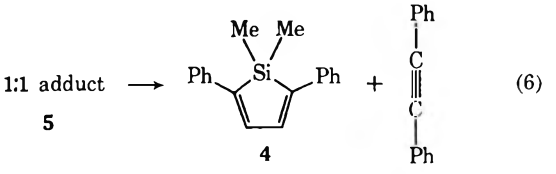


3 9 8 (5)

similar reactions for other 7-silanorbornadienes (eq 1 and 2). In fact, the yield of 1,1,4,4-tetramethyl-2,3,5,6 tetraphenyl-1,4-disilacyclohexa-2,5-diene (**8**) is as good as that reported for the copyrolysis of other 7,7-dimethyl-7-silanorbornadienes with tolan.[3] The formation of **8** does indicate that adduct **5** is either 7-silanorbornadiene **3** or that, under pyrolytic conditions, it goes to **3** at least as an unstable intermediate. This conclusion is further substantiated by the formation of 1,2,3,4-tetraphenylbenzene (**9**) in a good yield, since substituted naphthalenes and benzenes have been shown to be by-products when 7-silanorbornadienes are pyrolyzed to give dimethylsilylene[3] (eq 1 and 2).

The exact nature of adduct **5** at high temperatures is given by mass spectrometry and the pyrolytic reactions other than the one discussed above. In fact, the mass spectrum and high vacuum pyrolytic decomposition reactions of **5** show that it also undergoes disassociation in the gas phase.

The pyrolysis of the 1:1 adduct by itself in a sealed tube gives mainly disilacyclohexadiene **8** and tetraphenylbenzene. The formation of **8** indicates that some of the 1:1 adduct disassociates to give silacyclopentadiene **4** and tolan (eq 6). The tolan then reacts



4 (6)

with dimethylsilylene from the decomposition of 7-silanorbornadiene **3** to give disilacyclohexadiene **8** (eq 7 and 8). The tetraphenylbenzene is formed as a by-product of the elimination of dimethylsilylene from 7-silanorbornadiene **3** (eq 7). The copyrolysis of the 1:1 adduct with butadiene **7** to give silacyclopentadiene **4**, disilacyclohexadiene **8**, tetraphenylbenzene **9**, silabicyclononadiene **6**, and 1,1,3,4-tetramethyl-1-silacyclopent-3-ene (**10**) further indicates that adduct **5** disassociates and also forms 7-silanorbornadiene **3** in a sealed tube at 300°. The main products which are

(7) W. H. Atwell, D. R. Weyenberg, and H. Gilman, *J. Org. Chem.*, **32**, 885 (1967).

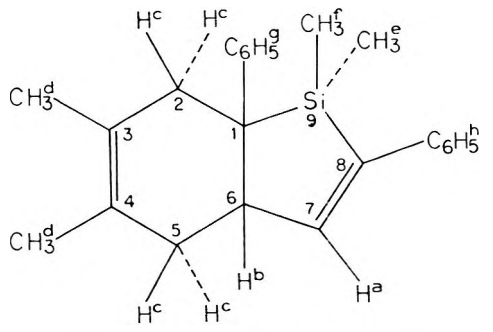
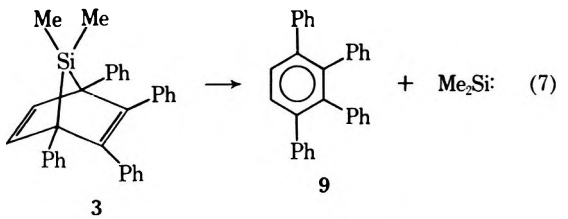


Figure 1.—1,8-Diphenyl-3,4,9,9-tetramethyl-9-silabicyclo[4.3.0]-nona-3,7-diene (6).



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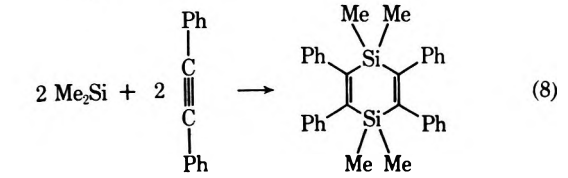

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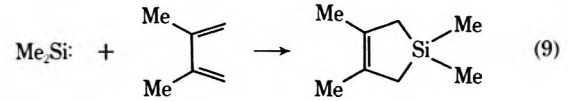
formed in this pyrolysis can be explained by the simultaneous occurrence of reactions given by eq 6–9 and 4.



7 10

The reaction of 2,3-dimethyl-1,3-butadiene with dimethylsilylene[5] (eq 9) has been reported and the reaction of 1,1-dimethyl-2,5-diphenylsilacyclopentadiene with 2,3-dimethyl-1,3-butadiene (eq 4) will be discussed below.

Although the structure of the 1:1 adduct of 1,1-dimethyl-2,5-diphenyl-1-silacyclopentadiene with tolan in the solid state cannot be determined from the data collected during this investigation, it certainly appears to be a very interesting material. If it is 7-silanorbornadiene **3**, it is very unstable with respect to a retro-Diels–Alder reaction. If it is not a 7-silanorbornadiene, but some other type of adduct, to the best of our knowledge it is the only reported example of a stable adduct between an alkyne and a silane. Speculation about the possible bonding in this adduct will be resisted since an X-ray structural determination will be necessary to prove the structure and such an investigation is underway.[8] However, data obtained during this investigation does show that adduct **5** dissociates to a 1:1 molar mixture of silacyclopentadiene **4** and tolan in solution and in the gas phase at low pressure. In a sealed tube at high temperature where both gas and liquid phase are present, the 1:1 adduct exists as a complex mixture of silacyclopentadiene **4**, tolan, and 7-silanorbornadiene **3**.

The reaction of 1,1-dimethyl-2,5-diphenyl-1-silacyclopentadiene with 2,3-dimethyl-1,3-butadiene to give silabicyclononadiene **6** is rather surprising because, to give this product, silacyclopentadiene **4** is reacting as a dienophile and butadiene **7** as diene. In fact, this reaction proceeds very well at 200° to give a 62% yield of **6**. The assignment of the 9-silabicyclo[4.3.0]nonadiene structure to **6** was made mainly from ^{1}H nmr and mass spectral data.

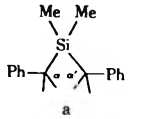
The mass spectrum of silabicyclononadiene **6** has large peaks at m/e 91, 105, 121, 135, and 145. Most of these peaks are found to be major ones in the spectra of organosilicon compounds which have two phenyl groups α and α' to a dimethylsilicon functional group.[9] An assignment of the ^{1}H nmr is given below using the lettering system in Figure 1.

The phenyl protons H^g and H^h, having a total relative intensity of 10, give rise to the multiplet at τ 2.80. This multiplet appears to be made up of two separate resonances separated by about 2 cps. The multiplet observed at τ 3.29 and having a relative intensity of 1 H is assigned to the olefinic proton H^a. This olefinic proton falls τ 0.6 upfield from those in **4** which fall under the aromatic resonances. The resonance assigned to H^a is, however, about where one would expect to find it for an olefinic proton on a small-ring olefinic compound.[10] The multiplet at τ 6.51 has a relative intensity of 1 H and is assigned to the remaining methine proton H^b. The very broad, 60-cps, ill-defined multiplet centered about τ 7.85 has been assigned to the four methylene protons H^c. The resonances due to these protons would be expected to be ill-defined since two of them are unequally shielded by the phenyl ring at the 1 position and the other two are unequally coupled to proton H^b. The singlet at τ 8.39 having a relative intensity of 6 H is exactly where expected for olefinic methyl protons[10] and this singlet is assigned to H^d. The remaining two singlets at τ 9.61 and 10.07 have relative intensities of 3 H each and are assigned to H^e and H^f, respectively. The H^f protons would be expected to fall at a higher field than H^e since the former are on the same side of the five-membered ring as the phenyl group at the 1 position and a model shows that these protons lie in the shielding zone of the phenyl group.[11] The 9-silabicyclononadiene structure given for **6** is indeed consistent with the data available.

The product of the reaction of silacyclopentadiene **4** as the diene with 2,3-dimethyl-1,3-butadiene as the dienophile would have structure **11**. It is easy to see that this structure does not fit the observed ^{1}H spectrum since the ten types of protons in structure **11** should give a ^{1}H spectrum with distinct resonances having relative intensities of 10:2:2:2:3:3:3:3 as you go from low field to high field. The observed spectrum has relative intensities of 10:1:1:4:6:3:3. The product from the

(8) T. J. Barton, personal communication.

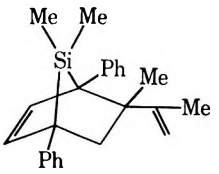
(9) During the course of investigating the properties of several organosilicon compounds with phenyl groups α and α' to a dimethylsilicon group (see structure a), it was observed that most or all of the above peaks were major contributors to the mass spectra of all these compounds.



a

(10) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 138.

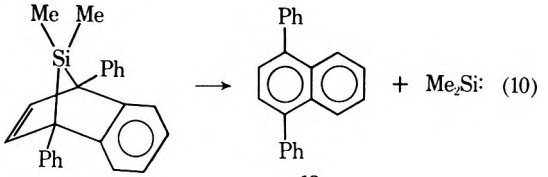
(11) The model was constructed from CPK space filling models and the stereochemistry assumed was that expected for maximum overlap of unsaturation in the transition state for the Diels–Alder reaction.



11

Diels–Alder reaction of 1,1-dimethyl-2,5-diphenyl-1-silacyclopentadiene with 2,3-dimethyl-1,3-butadiene is thus concluded to be the silabicyclononadiene **6**.

The attempted synthesis of 2:3-benzo-7,7-dimethyl-1,4-diphenyl-7-silanorbornadiene (**12**) appears to shed some light on the decomposition of other 7-silanorbornadienes. In an attempt to prepare 7-silanorbornadiene **12** by the procedure used to prepare **1**,[3] the products isolated and identified were diphenylnaphthalene **13** and a siloxepinone.[12] The substituted naphthalene **13** is the expected product for the elimination of dimethylsilylene from 7-silanorbornadiene **12** according to eq 10. It appears, then, that **12** is not



12 13

$$\text{12} \rightarrow \text{13} + Me_2Si: \quad (10)$$

stable and eliminates dimethylsilylene under preparative conditions were a maximum temperature of 68° was encountered. This is somewhat surprising since 7-silanorbornadienes **1** and **2** must be heated to between 200 and 300° to effect dimethylsilylene elimination. One explanation for this is that the four adjacent phenyl groups in **1** and the five adjacent ones in **2** give these compounds large activation energies for elimination of dimethylsilylene. This would be expected if the activated complex for elimination has a planar structure similar to the structure of the products, since a planar activated complex would force the four or five adjacent phenyl groups very close together. However, 7-silanorbornadiene **12** has isolated phenyl groups and can attain a planar structure more easily, giving a lower activation energy and a more facile elimination of dimethylsilylene.

From the data given here it is apparent that the Diels–Alder behavior of 1,1-dimethyl-2,5-diphenyl-1-silacyclopentadiene (**4**) is quite varied. It readily undergoes a reaction with tolan to give a 1:1 adduct which can go to 7-silanorbornadiene **3** or dissociate to give silacyclopentadiene **4** and tolan back again. With benzyne as dienophile, 7-silanorbornadiene **12** is formed but is so unstable that it readily eliminates dimethylsilylene to give the substituted naphthalene **13**. The reaction of **4** with butadiene **7** indicates that **4** can also react as a dienophile. Further studies of Diels–Alder reactions of silacyclopentadienes and the nature of the products formed in these reactions are now underway.

(12) T. J. Barton, A. J. Nelson, J. Clardy, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 14, 1970, or *Chem. Eng. News*, **48**, 36 (1970). This recent preliminary report indicates that **12** can be formed at low temperatures, but that it decomposes, according to eq 10, below room temperature, thus substantiating the conclusions drawn here. However, when the preparation of **12** was carried out by Dr. Barton using a method different from ours, it underwent further reaction with the benzyne intermediate to give a siloxepinone. After Barton's report appeared, we were also able to identify this siloxepinone as a product of our reaction.

Experimental Section

Instrumentation.—Infrared spectra were recorded using a Perkin-Elmer Model 237b Infracord and were standardized against polyethylene. The peaks are reported in reciprocal centimenters with S = strong, M = medium, and W = weak absorbances. Melting points were obtained on a Thomas-Hoover melting point apparatus and are reported uncorrected. The ultraviolet spectra were determined using a Cary Model 14 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Jeolco C-60H spectrometer using dichloromethane as the primary reference. The chemical shifts reported are relative to tetramethylsilane and have been corrected for solvent effects to the primary reference signal.

The mass spectra were obtained using a Hitachi RMU-6H mass spectrometer. Only the parent peak, base peak, and other important peaks are reported here. A detailed examination of the mass spectra of these organosilicon compounds will be published elsewhere. Elemental analysis of the compounds was done by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

Materials.—Dichlorodimethylsilane (Matheson), diphenylacetylene (Aldrich), styrene (Matheson), 2,3-dimethyl-1,3-butadiene (Aldrich), petroleum ether (bp 60–90°) (Matheson), and hexane (Matheson) were used without further purification. All other solvents were dried over lithium aluminum hydride, barium oxide, or phosphorus pentoxide and distilled before use.

Preparation of 1,1-Dimethyl-2,5-diphenyl-1-silacyclopentane (14).—This compound was prepared by a previously reported procedure.[10] Vacuum distillation of the reaction mixture at 0.25 Torr gave a 65% yield of silacyclopentane **14** and a dark brown sticky, oily residue. After purification of 1,1-dimethyl-2,5-diphenyl-1-silacyclopentane by a triple vacuum distillation, the following physical data were determined: bp 120–130° (0.25 Torr) [lit.[13] 137–150° (0.3–0.4 Torr)]; $n^{25}D$ 1.5759 (lit.[13] 1.5740); ^1H nmr (60 MHz, CCl_4) three singlets at τ 10.37, 9.90, and 9.47 (total 6 H), 7.50 (m, 6 H), 2.70 (m, 10 H); mass spectrum (80 eV) m/e (rel intensity) 266 (75) P, 117 (100); uv max (cyclohexane) 230 nm (ϵ 25,000), 254 (940), 269 (1000), 277 (720); ir 3106 (W), 3086 (W), 3040 (M), 2941 (M), 2865 (M), 1942 (W), 1866 (W), 1799 (W), 1733 (W), 1600 (S), 1580 (W), 1493 (S), 1449 (M), 1406 (W), 1348 (W), 1300 (W), 1248 (S), 1208 (M), 1152 (W), 1109 (W), 1092 (M), 1073 (M), 1031 (M), 1000 (W), 971 (W), 945 (W), 901 (M), 849 (S), 826 (S), 794 (S), 776 (S), 758 (S), 746 (S), 698 (VS).

Preparation of 1,1-Dimethyl-2,5-diphenyl-1-silacyclopentadiene (4).—Silacyclopentadiene **4** was prepared by bromination of silacyclopentane **14** with *n*-bromosuccinimide followed by dehydrobromination using sodium acetate as described previously.[7] After addition of the dehydrobromination reaction product mixture to twice its own volume of a 50:50 ethanol–water mixture, an 82% yield of silacyclopentadiene **4** was isolated by filtration. Purification of this silacyclopentadiene **4** by recrystallization from acetone yielded a material which gave the following physical data: mp 133–134° (lit.[7] 130–133°); ^1H nmr (60 MHz, CCl_4) τ 9.44 (s, 6 H), 2.68 (m, 12 H); mass spectrum (80 eV) m/e (rel intensity) 262 (100) P; uv max (cyclohexane) 229 nm (ϵ 13,200), 375 (20,000) [lit.[6] 230 (13,000), 370 (20,000)]; ir (KBr pellet) 3058 (W), 3040 (W), 2976 (W), 2907 (W), 1949 (W), 1873 (W), 1739 (W), 1590 (S), 1572 (M), 1488 (S), 1441 (S), 1410 (W), 1321 (M), 1299 (W), 1276 (W), 1259 (W), 1244 (S), 1155 (W), 1100 (W), 1073 (M), 1028 (M), 979 (W), 929 (S), 868 (S), 847 (W), 831 (S), 791 (S), 773 (VS), 749 (S), 691 (S), 638 (M).

Anal. Calcd for $C_{18}H_{18}Si$: C, 82.5; H, 6.88; Si, 10.7. Found: C, 82.6; H, 6.85; Si, 10.5.

Preparation of the 1:1 Adduct of 1,1-Dimethyl-2,5-diphenyl-1-silacyclopentadiene with Tolan (5).—In a typical preparation of adduct **5**, 0.78 g (3.0 mmol) of silacyclopentadiene **4** and 0.79 g (4.4 mmol) of tolan were dissolved in 60–90° boiling petroleum ether and, upon cooling, 0.78 g (1.8 mmol) of crystalline adduct **5** was isolated by filtration and was purified by recrystallization from the same solvent. Material prepared and purified by this procedure gave the following physical data: mp 101–102°; ^1H nmr (60 MHz, CCl_4) τ 9.31 (s, 3 H), 2.69 (m, 11 H); mass

(13) D. R. Weyenberg, L. H. Toporcer, and A. E. Bey, *J. Org. Chem.*, **30**, 4096 (1965).

spectrum (80 eV) m/e (rel intensity) 262 (100), no parent peak was observed; uv max (cyclohexane) 265 nm (ϵ 22,200), 273 (22,800), 281 (30,000), 289 (20,500), 298 (26,600), 375 (19,000); ir (KBr pellet) 3067 (W), 3040 (W), 2976 (W), 1961 (W), 1890 (W), 1602 (W), 1590 (W), 1570 (M), 1497 (M), 1490 (S), 1445 (S), 1406 (W), 1319 (M), 1274 (W), 1250 (S), 1182 (W), 1179 (W), 1161 (W), 1100 (W), 1073 (M), 1022 (M), 997 (W), 988 (W), 927 (M), 917 (W), 908 (W), 868 (S), 850 (W), 833 (S), 792 (M), 776 (VS), 756 (VS), 746 (S), 692 (S), 686 (S), 633 (M).

Anal. Calcd for $C_{32}H_{28}Si$: C, 87.3; H, 6.37; Si, 6.37. Found: C, 87.2; H, 6.43; Si, 6.49; mol wt (benzene solution, 42°, by vapor pressure osmometry), 229.

Pyrolysis of Adduct 5 in the Presence of Tolan.—A 0.97-g (2.3 mmol) sample of **5** and 1.11 g (6.2 mmol) of tolan were sealed, under vacuum, in a pyrex tube and then pyrolyzed at 300° for 16 hr. The tube was opened and the pyrolysis residue dissolved in hot benzene. Then petroleum ether (bp 60–90°) was added to the benzene solution, at reflux, until precipitation occurred. A white polymeric material, 0.24 g, was collected by filtration after the solution had been cooled to 0°. The solvent was removed from the filtrate and the residue thus received was fractionally recrystallized from petroleum ether to give 0.27 g (51%) of disilacyclohexadiene **8** and 0.75 g (87%) of tetraphenylbenzene **9**.

When 1,1,4,4-tetramethyl-2,3,5,6-tetraphenyl-1,4-disila-2,5-cyclohexadiene (**8**) was purified by sublimation at 140° under high vacuum (10^{-6} Torr), it gave the following physical data: mp 315 ± 5° (lit.[3] 323–326°); ^{1}H nmr (60 MHz, CS_2) τ 3.15 (m, 20 H), 9.92 (s, 12 H); mass spectrum (80 eV) m/e (rel intensity) 472 (36) P, 73 (100); uv (cyclohexane) no distinct max, just an increasing absorption from 300 to 220 nm; ir (KBr pellet) 3086 (W), 3030 (W), 2976 (W), 1946 (W), 1872 (W), 1801 (W), 1597 (W), 1575 (W), 1481 (M), 1439 (M), 1414 (W), 1326 (W), 1250 (S), 1242 (S), 1185 (W), 1156 (W), 1070 (M), 1029 (W), 996 (M), 911 (W), 883 (S), 834 (S), 797 (M), 769 (S), 752 (S), 721 (M), 696 (VS), 662 (S).

Anal. Calcd for $C_{32}H_{32}Si_2$: C, 81.3; H, 6.78; Si, 11.9. Found: C, 81.4; H, 6.78; Si, 11.7.

Pyrolysis of Adduct 5 in a Sealed Tube.—A 0.50-g sample of **5** was sealed, under vacuum, in a 50-ml pyrex tube and pyrolyzed at 300° for 24 hr. The tube was cooled and opened, and the solid product mixture was fractionally recrystallized from petroleum ether (bp 90–120°). The first fraction of crystals, which were insoluble in hot 90–120° petroleum ether, was identified, by comparison of its properties with those of an authentic sample, as 1,4-disilacyclohexadiene **8**. This fraction amounted to an estimated 10% yield. Then several fractions of tetraphenylbenzene **9** were recovered and identified as such by melting point,[14] mass spectral, infrared, nuclear magnetic resonance, and elemental analysis. After recovery of as much **9** as possible, the petroleum ether filtrate was red brown and appeared to be similar to the dimethylsilicon polymer solutions described previously.[3]

Pyrolysis of Adduct 5 under High Vacuum. Method A.—A piece of pyrex tubing 60 cm long and 25 mm in diameter was sealed on one end and affixed with a joint at the other. The sealed end of the tube was charged with 0.85 g of **5** and the tube placed in a 30-cm horizontal tube furnace, such that the sealed end with sample was outside the oven. The tube was connected to the high vacuum system, evacuated to 10^{-6} Torr and the oven heated to 200°. After the temperature had reached equilibrium, the furnace was slowly moved toward the sample until, after 48 hr, the sample was just inside the open end of the furnace where the temperature was 50–70°. At this time, the pyrolysis was stopped and three bands of crystals were observed in the tube. The first band, 0.47 g, was where starting sample had been placed and was identified as an approximately 1:1 mixture of silacyclopentadiene **4** and adduct **5** by comparison of its ir with that of a known 1:1 mixture. The second band, 0.17 g, was just outside the exit end of the furnace and was identified as 1:1 adduct **5**. The third band, 0.17 g, was about 20 cm from the exit end of the furnace and was identified as tolan.

Method B.—A sublimator was charged with about 1 g of adduct **5** and heated to 50° under high vacuum. After 24 hr under these conditions, the sublimator was opened, the sublimate was shown to be tolan, and the residue was identified as pure silacyclopentadiene **4**.

(14) M. Tsutsui and H. Zeiss, *J. Amer. Chem. Soc.*, **81**, 6090 (1959).

Pyrolysis of Adduct 5 in the Presence of 2,3-Dimethyl-1,3-butadiene 7.—A 100-ml pyrex bomb fitted with a break tip seal was charged with 0.72 g (1.63 mmol) of **5** and 0.37 g (4.5 mmol) of **7**. The tube was evacuated, sealed, and then placed in an oven at 300° for 16 hr. Upon cooling, the tube was connected to the high vacuum system and opened, and all volatile products were removed, leaving behind only the nonvolatile products. The volatile products were separated by trap-to-trap fractionation and were identified by mass spectrometry and gas chromatography as silacyclopentene **10** (0.05 g),[5] unreacted butadiene **7** (0.20 g), and a dimer of butadiene **7** (trace).

Hot *n*-hexane was added to the nonvolatile material from the vacuum fraction. This gave a reddish-brown solution and a white precipitate. The precipitate was identified by ir, nmr, and mass spectrometry as tetraphenylbenzene **9** (0.21 g) and 1,4-disilacyclohexadiene **8** (0.09 g). The reddish-brown solution was subjected to gas chromatographic analysis using an SE-30 silicon gum rubber column maintained at 210°. Using these conditions and by changing the flow rate of carrier gas, it was possible to to observe at least 15 peaks; however, the peaks due to four compounds made up more than 75% of the integrated total of all the peaks. These four compounds were identified by ir, mass spectrometry, and vpc retention times as silabicyclononadiene **6** (50%), silacyclopentadiene **4** (10%), an unknown material having a parent m/e of 264 (7%), and a second unknown compound having a parent m/e of 258 (8%). Because of the extreme complexity of this reaction and difficulty in separating and identifying products, absolute percentage yields for the major products were not determined.

Reaction of Silacyclopentadiene 4 with Butadiene 7. Preparation of Silabicyclononadiene 6 in Good Yield.—A pyrex pyrolysis tube was charged with 1.01 g (3.9 mmol) of silacyclopentadiene **4** and 4.5 mmol of butadiene **7**. The tube was sealed under high vacuum and placed in a furnace at 200° for 48 hr. Upon cooling, the tube was opened; unreacted butadiene was removed under high vacuum and the solid residue was taken up in hot *n*-hexane. After cooling the *n*-hexane solution, 0.83 g (62%) of pure white silabicyclononadiene **6** was collected by filtration. When **6** was purified by a second recrystallization from *n*-hexane, it gave the following physical data: mp 115–116°; ^{1}H nmr (60 MHz, CCl_4) τ 10.07 (s, 3 H), 9.61 (s, 3 H), 8.38 (s, 6 H), 7.85 (m, 4 H), 6.51 (m, 1 H), 3.29 (m, 1 H), 2.80 (m, 10 H); mass spectrum (80 eV) m/e (rel intensity) 344 (25) P, 262 (100); uv max (cyclohexane) 256 nm (ϵ 14,000); ir (KBr pellet) 3067 (W), 3030 (W), 3012 (W), 2994 (M), 2976 (W), 2941 (M), 2890 (M), 2874 (M), 2841 (M), 1949 (W), 1876 (W), 1799 (W), 1595 (S), 1572 (M), 1497 (M), 1493 (S), 1447 (S), 1431 (M), 1406 (W), 1372 (W), 1339 (W), 1302 (W), 1287 (W), 1250 (S), 1209 (W), 1192 (W), 1181 (W), 1149 (W), 1124 (W), 1112 (W), 1101 (W), 1063 (W), 1042 (W), 1031 (W), 1007 (W), 998 (W), 974 (W), 935 (M), 923 (W), 910 (W), 888 (M), 876 (S), 857 (M), 835 (S), 828 (S), 790 (S), 780 (S), 771 (S), 754 (S), 742 (S), 696 (VS), 662 (W), 637 (M).

Anal. Calcd for $C_{24}H_{28}Si$: C, 83.9; H, 8.15; Si, 8.19. Found: C, 84.4; H, 8.18; Si, 8.19.

The above reaction did not go when carried out in dyglyme solvent at 100, 150, 200, or 250°. When it was attempted without solvent at 300°, the result was such a complex mixture that attempts to isolate and identify all products failed. However, no products were isolated and identified which indicated dimethylsilylene elimination. In particular, none of silacyclopentene **10** could be isolated.

An Attempted Preparation of 2:3-Benzo-7,7-dimethyl-1,4-diphenyl-7-silanorbornadiene (12).—The procedure used was the same as the one reported in the literature[3] for the preparation of 2:3-benzo-7-silanorbornadiene **1** except that silacyclopentadiene **4** was used instead of 1,1-dimethyl-2,3,4,5-tetraphenyl-1-silacyclopentadiene. Anthranilic acid (4.0 g) and 6.0 g of isoamyl nitrite were dissolved in 60 ml of dry THF. These solutions were then added simultaneously over a period of 2.5 hr to 2.9 g of silacyclopentadiene **4** dissolved in gently refluxing dry THF. After addition of anthranilic acid and isoamylnitrite was completed, the solution was refluxed for an additional 2 hr. The solvent was removed from the reaction mixture and the residue was then subjected to column chromatography using neutral alumina as packing and petroleum ether (bp 60–90°) to develop the column. The products isolated and identified from this separation were substituted naphthalene **13** and a siloxepinone.[12] Other fractions were obtained from the column fractionation; however, they appeared to be polymeric as mass spectra could

not be obtained for these materials even when they were heated 200° in the inlet system of the mass spectrometer.

Registry No.—**4**, 7688-03-1; **5**, 28861-05-4; **6**, 28861-04-3; **8**, 751-37-1; **14**, 2762-95-0; diphenylacetylene, 501-65-5; 2,3-dimethyl-1,3-butadiene, 513-81-5; benzyne, 462-80-6.

Acknowledgment.—We thank P. Maruca and L. Roseman for assistance in the laboratory and Drs. J. Grunwell and R. Schaeffer for valuable discussions. We also gratefully acknowledge The Research Corporation for partial financial support of this research.

Steric Deshielding in Nonrigid Systems. II.[1] The Preparation and Nuclear Magnetic Resonance Spectra of the Hexachlorocyclopentadiene Adducts of 1,3-Alkadienes

CARLOS G. CÁRDENAS

Organic Chemicals Group, Glidden-Durkee, Division of the SCM Corporation, Jacksonville, Florida 32201,[2] and Research Division, Phillips Petroleum Company, Bartlesville, Oklahoma 74003

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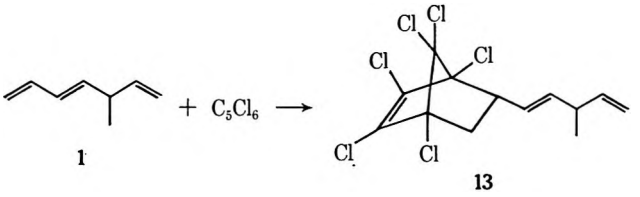
Hexachlorocyclopentadiene is remarkably regiospecific in its reaction with olefins, reacting more readily with terminal than with internal olefins and more readily with conjugated than with isolated olefins. A steric deshielding mechanism is invoked to account for the difference in the nmr spectra of the adducts of *cis*- and *trans*-1,3-alkadienes. The mechanism is extended to include the deshielding of allylic protons by *cis*-alkyl substituents in rigid and nonrigid systems.

Hexachlorocyclopentadiene (C_5Cl_6) is a well-known and very reactive diene in Diels–Alder chemistry. Its reactions have been well studied and have led to the synthesis of many interesting and useful hexachlorobicyclo[2.2.1]heptenes.[3] It reacts readily under mild conditions even with "unactivated" olefins but differs from the typical Diels–Alder diene in that it has been shown to have an "inverse electron demand;" that is, it reacts preferentially with electron-rich dienes and not at all with tetracyanoethylene.[4] This characteristic may be associated with the concept of "spiroconjugation" as described by Simmons and Fukunaga.[5]

We have studied the reaction of C_5Cl_6 with various 1,3-alkadienes and have found that the reaction is remarkably regiospecific. Hexachlorocyclopentadiene reacts more readily with a conjugated than with an isolated olefin and more readily with a terminal than with an internal olefin giving good yields of single products. Moreover, we have found that a diene capable of assuming a cisoid geometry is more reactive than one for which this conformation is disfavored.[6] In addition, the nmr spectra of the products have proven interesting and very useful in determining the geometry of the double bond adjacent to the bicyclic moiety.

Regiospecificity.—Reaction of 5-methyl-1-*trans*-3,6-heptatriene (**1**) with C_5Cl_6 for 6 hr at 90° gives a single product (**13**) in 84% yield. The ultraviolet spectrum of **13** shows no absorption characteristic of a conjugated diene [for **1**, λ_{max} 227 nm (log ϵ 4.40)].[7] Thus, the reaction occurs at one of the conjugated double bonds. The appearance of five olefinic protons in the nmr spectrum shows that it is the terminal, conjugated double bond that reacts. Examination of the spectra of the products derived from 1,3,7-octatriene (**2**) and 1,3,6-octatriene (**3**) showed that here, also, reaction occurs exclusively at the terminal, conjugated double bond. The



1 13

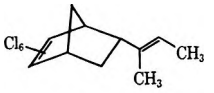
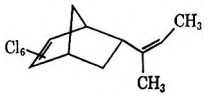
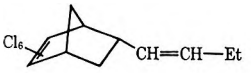
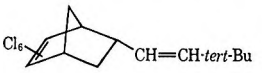
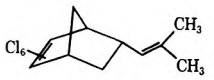
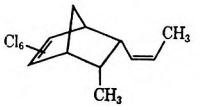
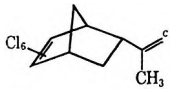
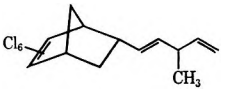
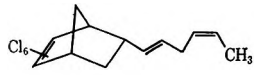
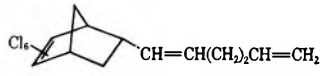
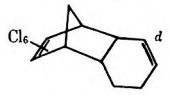
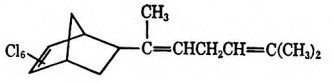
generality of this regiospecificity was shown by examination of a series of 1,3-alkadienes (see Table I). With only one exception, the reaction occurs exclusively at the terminal position. In the case of *cis*-1,3-pentadiene, about 7% of the alternate product is apparent from the presence of a doublet (J = 7.0 Hz) at τ 9.04 in the nmr spectrum.

Specificity in the reaction of C_5Cl_6 with monoolefins was also demonstrated by treating *trans*-1,4,9-decatriene with an excess of the halocarbon. The only product isolated (~60% yield of recrystallized material) exhibits a 1.8-proton multiplet at τ 4.5–4.8 and analyzes correctly for the 2:1 product. Therefore, reaction occurs specifically to give the terminal diadduct. A brief study of *cis*-1,5,9-decatriene indicated that here, also, reaction occurs exclusively at the terminal sites.

Considering the "inverse electron demand" of C_5Cl_6, one would expect conjugation to decrease reactivity and, furthermore, one would expect alkyl substitution to increase reactivity. In both instances, the reverse has been found to be true. Although electronic effects are undoubtedly important in this reaction, they are handily outweighted by steric factors.[8] In the case of conjugation, the decrease in electron density caused

(1) Part I: C. G. Cárdenas, *Tetrahedron Lett.*, 4013 (1969).
(2) Address correspondence to author at Glidden-Durkee.
(3) H. E. Ungnade and E. T. McBee, *Chem. Rev.*, **58**, 249 (1958).
(4) J. Sauer and H. Wiest, *Angew. Chem. Int. Ed. Engl.*, **1**, 269 (1962).
(5) H. E. Simmons and T. Fukunaga, *J. Amer. Chem. Soc.*, **89**, 5208 (1967).
(6) The role of secondary orbital interactions when reaction occurs adjacent to an unsaturated site has been discussed previously: C. G. Cárdenas, *Chem. Commun.*, 134 (1970).
(7) S. Tanaka, K. Mabuchi, and N. Shimazaki, *J. Org. Chem.*, **29**, 1626 (1964).
(8) (a) W.-H. Chang, *J. Chem. Soc.*, 2305 (1965); (b) K. L. Williamson, Y.-F. Li Hsu, R. Lacko, and C. H. Youn, *J. Amer. Chem. Soc.*, **91**, 6129 (1969).

TABLE I
STRUCTURE AND PROPERTIES OF C_5Cl_6 ADDUCTS

Starting material	Product	Compd	Yield, %	Bp, °C (mm)
trans-1,3-Pentadiene		4	88	87 (0.05)
cis-1,3-Pentadiene		5	80	94 (0.09)
trans-3-Methyl-1,3-pentadiene		6	80	94 (0.03)
cis-3-Methyl-1,3-pentadiene		7	80	93 (0.03)
1,3-Hexadiene[a]		8	80	97 (0.03)
5,5-Dimethyl-1,3-hexadiene[b]		9	82	97–99 (0.03)
4-Methyl-1,3-pentadiene		10	83	98 (0.09)
cis,cis-2,4-Hexadiene		11	62	92 (0.04)
Isoprene		12	74	84 (0.03)
5-Methyl-1-*trans*-3,6-heptatriene		13	84	104 (0.09)
1-*trans*-3-*cis*-6-Octatriene		14	46	111 (0.04)
1,3,7-Octatriene		15	69	104 (0.02)
1,3-Cyclohexadiene		16	74	*e*
β-Ocimene[f]		17	78	

[a] Consisting of 96.4% trans and 3.6% cis. [b] Consisting of 94.4% trans and 5.6% cis. [c] Velsicol Corp., British Patent 614,931 (1948); *Chem. Abstr.*, **43**, 4693*e* (1949). [d] R. Reimenschneider and B. E. Grabity, *Monatsh. Chem.*, **91**, 22 (1960); *Chem. Abstr.*, **54**, 22527*h* (1960). [e] Solid, mp 113–115°. [f] Consisting of 85.9% trans and 14.1% cis.

by an adjacent double bond is outweighed by the increased polarizability of the system which can better stabilize[8b] a polar transition state.[6,9]

Nmr Spectra.—Table II contains data describing the nmr spectra of some of the C_5Cl_6 adducts prepared in this study. The data for the adducts of *cis*-1,3-hexadiene, *cis*-5,5-dimethyl-1,3-hexadiene, and *cis*-β-ocimene are not complete since the measurements were made on mixtures enriched in the trans isomer. The chemical shifts and coupling constants were obtained by inspection of spectra obtained either on a Varian A-60 or a Hitachi R-20 spectrometer.

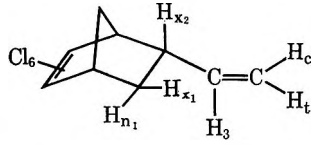
It is well known that in C_5Cl_6 derivatives as well as other bicyclo [2.2.1] systems exo protons appear at slightly lower field than their endo counterparts. The geminal coupling constant ($J_{n_1-x_1}$) should be of the order of 13 Hz[10−16] and the vicinal coupling con-

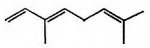
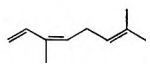
(9) After this paper was submitted for publication, a report appeared describing analogous but much less pronounced selectivity for the addition of dichlorocarbene, a less bulky electrophile, to similar systems. E. W. Duck, J. M. Locke, and S. R. Wallis, *J. Chem. Soc. C*, 2000 (1970).

(10) K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 516 (1963).
(11) K. L. Williamson, N. C. Jacobus, and K. T. Soucy, *ibid.*, **86**, 4021 (1964).
(12) D. F. O'Brian and J. W. Gates, Jr., *J. Org. Chem.*, **30**, 2593 (1965).
(13) M. M. Martin and R. A. Koster, *ibid.*, **33**, 3428 (1968).
(14) R. H. Cox and S. L. Smith, *J. Phys. Chem.*, **71**, 1809 (1967).
(15) R. G. Foster and M. C. McIvor, *Chem. Commun.*, 280 (1967).
(16) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967.

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF C_5Cl_6 ADDUCTS



Starting material	Product	Chemical shifts, τ						Coupling constants, Hz						
		H_{n1}	H_{x1}	H_{x2}	H_3	H_c	H_t	H_{n1}–H_{x1}	H_{n1}–H_{x2}	H_{x1}–H_{x2}	H_{x2}–H_3	H_3–H_t	H_3–H_c	H_c–H_t
	**4**	8.15	7.33	6.71	5.00	4.33	–CH_3 (8.31)	12.5	4.0	8.5	8.5		15.5	H_c–CH_3 6.0
	**5**	8.25	7.23	6.22	5.10	–CH_3 (8.27)	4.27	12.5	4.0	8.5	~9	~9	H_3–CH_3 1.5	H_t–CH_3 7.0
	**6**	7.87	7.40	6.64	–CH_3 (8.33)	4.5–4.9	–CH_3 (8.38)	12.5	5.0	8.5				H_c–CH_3 6.0
	**7**	7.84	7.41	5.95	–CH_3 (8.47)	–CH_3 (8.26)	4.38	13.0	5.0	8.5				H_t–CH_3 7
	*trans*-**8**	8.11	7.21	6.68	5.00	4.30	–Et (7.7–8.3, 9.02)	12.0	4.0	8.5	8.5		15.5	H_c–CH_2 6.0
	*cis*-**8**			~6.1										CH_2–CH_3 7.0
	*trans*-**9**	8.06	7.32	6.70	5.10	4.30	*tert*-Bu (9.00)	12.0	4.0	8.0	8.0		15.5	
	*cis*-**9**			~5.9										
	**10**	8.2	7.27	6.35	5.35	–CH_3 (8.2)	–CH_3 (8.2)	12.0	4.0	9.5	9.5			
	**11**	–CH_3 (9.08)	7.00	6.22	5.02	–CH_3 (8.29)	4.23	H_{x1}–CH_3 7.0		10.0	10.0	10.0	H_3–CH_3 1.5	H_t–CH_3 7.0
	**12**	7.87	7.36	6.72	–CH_3 8.15	4.9–5.4	4.9–5.4	13.0	4.5	9.0				
	*trans*-**17**	7.86	7.40	6.63[a]	–CH_3 8.1–8.6	4.7–5.2 (H_4, H_6)	–CH_2– 7.3	12.5	4.5	8.3				H_c–CH_2 ~7
	*cis*-**17**			5.94[a]										

[a] See Figure 1.

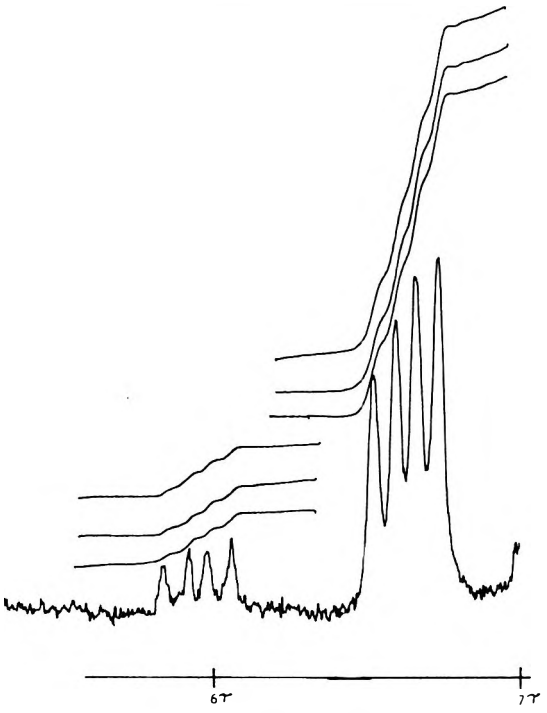
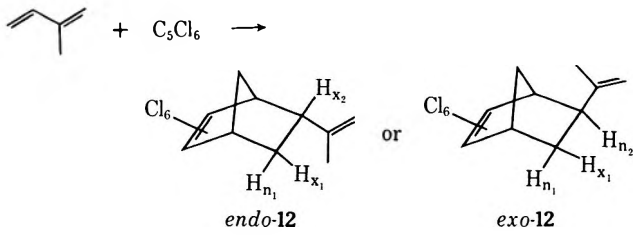


Figure 1.—The 60-MHz nmr signals assigned to H_{x_2} in the mixture of C_5Cl_6 adducts (**17**) of β-ocimene.

stants my be estimated from the Karplus curve[17] as $J_{x_1\text{-}x_2} \approx 8$ Hz and $J_{n_1\text{-}x_2} \approx 3$ Hz for an endo adduct and $J_{x_1\text{-}n_2} \approx 3$ Hz and $J_{n_1\text{-}n_2} \approx 8$ Hz for an exo isomer. Thus, for the isoprene adduct (*endo*-**12** or *exo*-**12**),

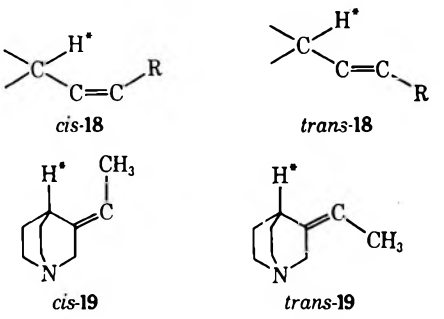


endo-**12** *exo*-**12**

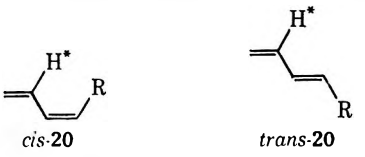
for example, we have an ABC system and can assign the chemical shifts and coupling constants by comparison with the predicted values. Examination of the spectrum provides the chemical shifts as given in Table II and $J_{n_1\text{-}x_1} = 13.0$, $J_{n_1\text{-vic}} = 4.5$, and $J_{x_1\text{-vic}} = 9.0$ Hz, in agreement with the expected endo structure of the adduct *endo*-**12**. Similar arguments were used to assign analogous structure to the other adducts.

The proton labeled as H_{x_2} (Table II) appears as a pair of doublets in cases such as **12** where H_3 = alkyl. When H_3 = H, however, $J_{x_2\text{-}H_3} \approx J_{x_1\text{-}x_2} \approx 9$ Hz and H_{x_2} appears as a pair of triplets. Of importance is the dependence of the chemical shift of H_{x_2} on the presence of an alkyl group in place of H_{cis}. *Thus, when adjacent to a trans or terminal olefin, H_{x_2} appears at τ ~6.7, whereas it is shifted to τ ~6.1 when adjacent to a cis or geminally disubstituted olefin.*

Analogous shifts have been reported for allylic methines in general (**18**, $\Delta\tau \approx 0.5$ ppm)[18-20] for the 3-ethylidene-1-azabicyclo[2.2.2]octanes (**19**, $\Delta\tau = 0.42$ ppm)[21]

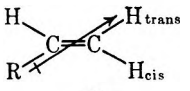


and for conjugated dienes (**20**, $\Delta\tau \approx 0.5$ ppm).[1] In



seeking an explanation for this effect we have considered various factors.

Group Dipole Effect.—The observation that in 1-alkenes H_{trans} is shielded with respect to H_{cis} (see **21**) has been attributed to the presence of a permanent



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dipole as drawn.[22] The effect is small, however, causing a chemical shift difference of <0.1 ppm for R = Me, Et, or *n*Bu in **21**. Accordingly H* in *trans*-**18** should experience a similar but diminished shielding effect with respect to H* in *cis*-**18**. The observed magnitude of the chemical shift difference, therefore, cannot be accounted for by this factor. In addition, it has been pointed out that allylic methylenes are affected much less ($\Delta\tau \approx 0.1$ ppm) and allylic methyls essentially not at all.[18,23] A group dipole effect would be expected to cause similar, if not greater, shifts as alkyl substitution on the carbon bearing H* is decreased.

Carbon–Carbon Double Bond Anisotropy.—The anisotropic effect of a carbon–carbon double bond has been the subject of some discussion.[25] Its applicability to the point in question[20] may be ruled out by a consideration of isomer pairs in which the position of the affected proton relative to the double bond remains unchanged. For example, in 3,5-cholestadiene introduction of a methyl group at C-6 serves to change the chemical shift of H-4 from τ 4.22 to 3.58.[1] Here H-4 retains

(17) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); A. Factor and T. G. Traylor, *J. Org. Chem.*, **33**, 2607 (1968), and references cited therein; and A. P. Marchand, N. W. Marchand, and A. L. Segre, *Tetrahedron Lett.*, 5207 (1970).

(18) F. C. Stehling and K. W. Bartz, *Anal. Chem.*, **38**, 1467 (1966).

(19) D. J. Frost and J. P. Ward, *Tetrahedron Lett.*, 3779 (1968).

(20) R. B. Bates, A. D. Brewer, B. R. Knights, and J. W. Rowe, *ibid.*, 6163 (1968).

(21) J. C. Nouls, G. Van Binst, and R. H. Martin, *ibid.*, 4065 (1967).

(22) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **83**, 231 (1961).

(23) In fact, the chemical shift difference for allylic methyls is reversed, a methyl cis to an alkyl group appearing at higher field than its counterpart.[18,24]

(24) R. Zurflüh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *J. Amer. Chem. Soc.*, **90**, 6224 (1968); W. S. Johnson, A. van der Gen, and J. J. Swoboda, *ibid.*, **89**, 170 (1967); and R. B. Bates and D. M. Gale, *ibid.*, **82**, 5749 (1960).

(25) A. A. Bothner-By and J. A. Pople, *Ann. Rev. Phys. Chem.*, **16**, 54 (1965); J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, **23**, 2357 (1967).

the same position with respect to the double bonds but is still deshielded τ 0.64. Further examples of analogous conjugated systems have been cited.[1] A monoolefinic isomer pair which may also be considered is the 3-ethylidene-1-azabicyclo[2.2.2]octane pair (**19**). These isomers have been characterized by means of the nuclear Overhauser effect.[21,26] The bridgehead proton (H*) maintains its position in space and is shifted downfield τ 0.42 in the cis isomer.

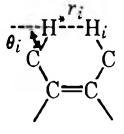
Carbon–Carbon Single Bond Anisotropy.—Having shown that the observed effect is not caused by the double bond, we may conclude that the deshielding effect is caused directly by the *cis*-alkyl group. For a proton in a rigid system as in **19**, the effect of the carbon–methyl single bond may be calculated using McConnell's relationship[27] along with the anisotropy terms provided by ApSimon, *et al.*[28] The net effect predicted is one of *shielding* in the cis isomer relative to the trans. Thus, it is unlikely that bond anisotropy is a cause of the observed effect.

Steric Deshielding.—An elegant discussion of the magnetic deshielding experienced by a spatially crowded hydrogen in a rigid system has been presented recently by Cheney.[29] Examples of systems experiencing this effect have been reviewed[29,30] and include various cage compounds and aromatics. Cheney has provided the empirical relation

$$\delta_s^{H^*} = -105 \sum_i \cos\theta \exp(-2.671 r_i)$$

wherein the steric shift ($\delta_s^{H^*}$) of the proton in question (H*) is related to the proximity (r_i) of the interacting nucleus (H_i) and the angel (θ_i) between the extension of the H_i–H* internuclear line and the H*–C bond.[29]

Although the nonrigidity of the compounds reported herein prevents the facile calculation of the expected steric shift, an estimate of a maximum shift of 0.5–0.6 ppm for $R_{cis} = CH_3$ can be made by considering only the most affected rotamer, *i.e.*, the rotamer having H* and H_i in the same plane and in closest proximity (see **22**). The magnitude of the observed shift will



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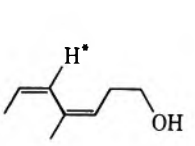
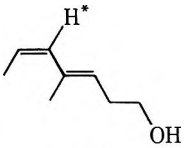
be affected by various factors, the more pertinent of which bear mentioning.

The size and nature of the *cis*-alkyl group will obviously affect the degree of deshielding. For example, a *cis-tert*-butyl group compared to a methyl group will provide significantly different values of both r_i and θ_i. Thus, the C_5Cl_6 adducts of the 5,5-dimethyl-1,3-hexadienes (Table II) show a larger deshielding effect on H* (H_{x_i}) than those of the 1,3-pentadienes (~0.8 *vs.* 0.49 ppm).

The importance of the distribution of rotamers should not be minimized. In a previous communication[1] we discussed a *cis*-alkyl steric shift in conjugated dienes (see **20**). The observed chemical shift difference for the isomer pairs considered ranges from 0.33 to 0.66 ppm. The one exception found was compound **23** which shows no effect. Examination of the uv spec-

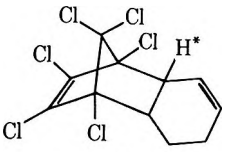


cis-**23**



trans-**23**

trum of *cis*-**23**, however, showed that no deshielding effect should be expected, since the low extinction coefficient (5850 *vs.* >17,000 for other similar dienes)[1] indicated a low concentration of planar rotamers. The C_5Cl_6 adduct **16** of 1,3-cyclohexadiene provides another example of a proton adjacent to a cis double bond which is not deshielded (τ_{H^*} = 6.5–7.0). Here,



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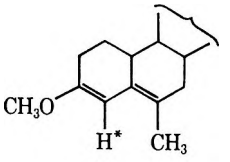
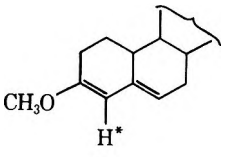
the *cis*-alkyl group, being part of a semirigid ring, cannot assume a deshielding position and no effect should be anticipated. In nonrigid molecules, the presence of alkyl groups on the carbon bearing H* (see **22**) serves to increase the H*–H_i interaction. Thus, the decrease in deshielding (*vide supra*) observed by Stehling and Bartz[18] for the series methine, methylene, and methyl is to be expected.

Since the mechanism of steric deshielding involves a van der Waals repulsion and a decrease in electron density at the deshielded site, substituents which can affect the charge distribution will be expected to alter the degree of observed deshielding. Thus, one finds that H* in **23** is deshielded by only 0.15 ppm when compared to H* in **24**.[1] The electron-donating effect



23



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of the methoxy substituent effectively reduces the expected electron drainage in H*. An analogous set of compounds without the methoxy substituent exhibit a deshielding effect of 0.64 ppm.[1]

Thus, we believe that the above cases represent examples of nonrigid molecules in which a spatially crowded proton is deshielded. The reliability of this effect is such that it may be employed as a tool in the determination of stereoisomerism. A family of compounds which exemplify its utility is the acyclic dimers of butadiene.

5-Methyl-1,3,6-heptatriene (**1**).—Infrared methods are often found to be unreliable for the determination of stereoisomerism in 1,3-alkadienes.[31] In the present case the carbon–hydrogen out-of-plane deformation

(26) F. A. L. Anet and A. J. R. Brown, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).
(27) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).
(28) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, **23**, 2339 (1967).
(29) B. V. Cheney, *J. Amer. Chem. Soc.*, **90**, 5386 (1968).
(30) J. G. Lindberg and A. G. Pinkus, *J. Magn. Resonance*, **1**, 652 (1969).
(31) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., p 46.

band for the trans olefin is shifted to higher frequency and is masked by the 990-cm^{-1} vinyl band. However, examination of the nmr spectrum of its C_5Cl_6 adduct **13** readily classifies **1** (as obtained from Monomer-Polymer Laboratories) as the trans isomer.

1,3,7-Octatriene (2).—Metal-catalyzed syntheses of 1,3,7-octatriene have been reported recently by Smutny[32] and by Takahashi.[33] These authors do not comment on the stereoisomerism of the triene although Butler and Brooks have reported syntheses of both isomers.[34] Examination of the spectrum of 1,3,7-octatriene provided by Smutny and Chung[32b] permits one to estimate an approximately equimolar distribution of cis and trans isomers.[1] Verification is obtained by treatment of the mixture with C_5Cl_6. The nmr spectrum of the crude product mixture exhibits six-line multiplets centered at τ 6.22 (H_{x_2} in the cis isomer) and at τ 6.63 (H_{x_2} in the trans isomer) in a ratio of 4:6.

1,3,6-Octatriene (3).—Various isomers of **3** are obtainable from butadiene depending upon the catalyst employed.[35] However, the nature of the internal double bond has never been rigorously defined and the possibility of 1,4,6-octatriene as an alternate structure has not been excluded, Reaction with C_5Cl_6 shows that the material provided by the Aldrich Chemical Co. consists solely of 1-*trans*-3-*cis*-6-octatriene (H_{x_2} = τ 6.67). On the other hand, dimerization of butadiene in the presence of a zero valent nickel complex in a hydroxylic solvent provides a mixture where the 1,3,6-octatriene fraction consists of two isomers different from the one described above. Preparation of the C_5Cl_6 adducts shows that the mixture consists of 1-*trans*-3-*trans*-6-octatriene and 1-*cis*-3,6-octatriene (H_{x_2} = τ 6.68 and 6.26, respectively).[36]

Experimental Section

All boiling points and melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer. Molecular weight determinations were made by vapor phase osmometry. Nmr measurements were made on a Varian A-60 or a Hitachi R-20 spectrometer.

The C_5Cl_6 adducts were prepared by stirring a solution (1:1) of the olefin and C_5Cl_6 under nitrogen in a glass-walled pressure vessel. Reactions were carried out at ~90° for 3–20 hr. The pure adduct was obtained by distillation or, in the case of **16**, recrystallization from CH_2Cl_2–EtOH. Molecular weight and elemental analyses of the adducts are listed in Table III. All C_5Cl_6 adducts studied exhibit a very strong single infrared band at ~6.20 μ in contrast to the bands at 6.24 and 6.36 μ[3] of pure C_5Cl_6. Descriptions of the nmr spectra not found in Table II are listed below and in Tables IV and V.

1,3-Cyclohexadiene Adduct (16).—The nmr spectrum consists of broad multiplets at τ 3.6–4.4, 6.5–7.2, and 7.7–8.8 in a ratio of 1.0:1.0:2.0.

trans-1,4,9-Decatriene Adduct.—Reaction of an equimolar solution of the triene and C_5Cl_6 for 21 hr at 90° provided an 81% conversion to a mixture of mono- and diadducts in 95% yield. The nmr spectrum of the crude product after removal of starting materials showed 3.9 olefinic protons, which, coupled with a molecular weight determination of 500 (calculated for monoadduct = 409, for diadduct = 682), suggests a 2:1 mixture of the monoadduct and the diadduct with all addition taking place at the terminal sites.

Anal. Calcd for a 2:1 mixture of $C_{15}H_{16}Cl_6$ and $C_{20}H_{16}Cl_{12}$: C, 40.05; H, 3.22. Found: C, 40.34; H, 3.12.

Treatment of 28.1 g of the above mixture with an additional 27.3 g (0.10 mol) of C_5Cl_6 for 15 hr at 100° provided the pure diadduct after recrystallization from pentane, mp 128–130°, mol wt 674. The nmr spectrum showed 1.8 olefinic protons in a

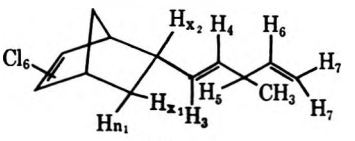
Table III

Analytical Data on C_5Cl_6 Adducts

Compd	Mol wt Calcd	Mol wt Found	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
4	341	340	35.2	34.9	2.4	2.5
5	341	360	35.2	35.1	2.4	2.3
6	355	357	37.2	37.2	2.8	2.8
7	355	350	37.2	37.1	2.8	2.8
8	355	351	37.2	37.1	2.8	2.9
9	383	382	40.8	40.7	3.7	3.6
10	355	358	37.2	36.6	2.8	2.8
11	355	357	37.2	36.9	2.8	2.9
13	381	390	41.0	41.0	3.2	3.2
14	381	381	41.0	41.3	3.2	3.3
15	381	382	41.0	40.7	3.2	3.3
16	353	356	37.4	37.7	2.3	2.3
17	409	411	44.0	44.2	3.9	3.9

Table IV

Nmr Data on the C_5Cl_6 Adduct of 5-Methyl-1-*trans*-3,6-heptatriene



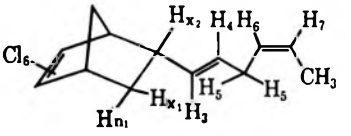
13

τ	Protons	Multiplicity[a]	Assignment	Coupling constants, Hz
4.0–4.6	2.1	m	H_4,H_6	H_{n_1}–H_{x_1} 12.5
4.8–5.3	2.9	m	H_5,H_7	H_{n_1}–H_{x_2}, 4.0
6.67	1.0	dt	H_{x_2}	H_{x_1}–H_{x_2}, 9.0
7.31	2.1	dd	H_{x_1}	H_{x_2}–H_3 9.0
7.2		s	H_5	H_4–H_5, ~7
8.08	1.0	dd	H_{n_1}	H_5–CH_3, 7.0
8.92	2.9	d	$-CH_3$	H_5–H_6, ~7

[a] d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, s = sextet.

Table V

Nmr Data on the C_5Cl_6 Adduct of 1-*trans*-3-*cis*-6-Octatriene[a]



14

τ	Protons	Multiplicity[b]	Assignment	Coupling constants, Hz
4.1–5.3	4.1	m	H_3,H_4,H_6,H_7	H_{n_1}–H_{x_2}, 12.0
6.69	1.1	dt	H_{x_2}	H_{n_1}–H_{x_2}, 4.0
7.31	3.0	dd	H_{x_1}	H_{x_1}–H_{x_2}, 8.5
7.1–7.6		m	H_5	H_{x_2}–H_3, 8.5
8.12	1.0	dd	H_{n_1}	H_7–CH_3, 6
8.41	2.8	d	$-CH_3$	

[a] The C_5Cl_6 adduct of the 1,3,6-octatriene mixture obtained from the dimerization of butadiene gave a similar spectrum wherein H_{x_2} appears at τ 6.26 and 6.68 in a ratio of ~3:7. These two doublets of triplets correspond to H_{x_2} adjacent to a cis and to a trans double bond, respectively. [b] See Table IV.

(32) (a) E. J. Smutny, *J. Amer. Chem. Soc.*, **89**, 6793 (1967); (b) E. J. Smutny and H. Chung, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, **14**, No. 2, B112 (1969).

(33) S. Takahashi, T. Shibano, and N. Hagihara, *Tetrahedron Lett.*, 2451 (1967).

(34) G. B. Butler and T. W. Brooks, *J. Org. Chem.*, **28**, 2699 (1963).

(35) H. Takahasi, S. Tai, and M. Yamaguchi, *ibid.*, **30**, 1661 (1965), and references cited therein.

(36) P. Heimbach, *Angew. Chem. Int. Ed. Engl.*, **7**, 882 (1968).

multiplet between τ 4.5 and 4.8, thus verifying that reaction had occurred exclusively at the terminal sites.

Anal. Calcd for $C_{20}H_{16}Cl_{12}$: C, 35.23; H, 2.37. Found: C, 35.4; H, 2.4.

Registry No.—**4**, 28861-35-0; **5**, 28861-36-1; **6**, 28861-37-2; **7**, 28861-38-3; *cis*-**8**, 28861-39-4; *trans*-**8**, 28861-40-7; *cis*-**9**, 28861-41-8; *trans*-**9**, 28861-42-9; **10**, 28861-43-0; **11**, 28861-44-1; **12**, 28861-45-2; **13**, 28861-46-3; **14**, 28861-47-4; **15**, 28861-48-5; **16**, 28861-49-6; *cis*-**17**, 28861-50-9; *trans*-**17**, 28861-51-0; *trans*-1,4,9-decatriene diadduct with hexachlorocyclopentadiene, 28861-52-1.

Acknowledgment.—The author is grateful to Mr. B. L. Martin and Mr. Paul Ciavolella for technical assistance.

Halogenated Ketenes. XXI. Cycloadditions with Carbonyl Compounds[1,2]

WILLIAM T. BRADY* AND LARRY SMITH

Department of Chemistry, North Texas State University, Denton, Texas 76201

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The cycloaddition of methyl-, chloro-, isopropyl-, and phenoxyketenes with chloral has been accomplished. Both *cis*- and *trans*-2-oxetanones were obtained in approximately equal amounts. The generation of dichloroketene by the dehalogenation of trichloroacetyl chloride in the presence of acetone and cyclohexanone, respectively, afforded these cycloadducts. Zinc appears to activate the carbonyl group, thus increasing the reactivity with dichloroketene. However, chloroketene forms only α,β-dichlorovinyl dichloroacetate under these conditions.

The cycloaddition of ketenes and carbonyl compounds to produce 2-oxetanones (β actones) dates back to the early investigations of Staudinger.[3] Most of the early work was with diphenylketene, and it was found that the addition of simple carbonyl compounds to diphenylketene did not normally proceed unless elevated temperatures were employed. Since the high temperatures required for cycloadditions polymerized aldoketenes and lower ketoketenes, early investigation were mostly limited to diphenylketene.[4]

Later the cycloaddition of ketene to aldehydes was found to proceed smoothly in ether in the presence of mild Friedel–Crafts type catalysts.[5] Ketones, however, required much stronger catalysts and more vigorous conditions to react with ketene.[6]

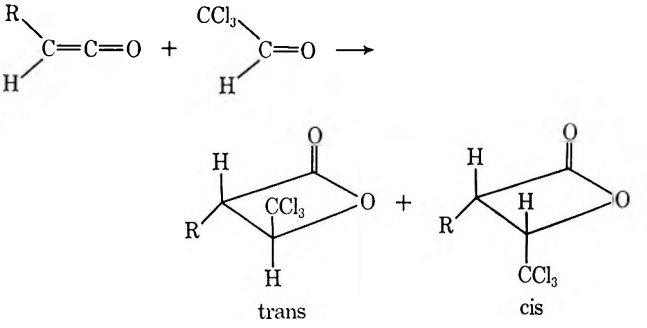
Borrmann and Wegler have recently reported that the cycloaddition of simple ketoketenes and carbonyl compounds is possible when the carbonyl compound is activated by electronegative substituents on the α carbon.[7] Thus, the cycloaddition of several ketenes to chloral were accomplished. The cycloadduct of dichloroketene and chloral was prepared by the *in situ* preparation of dichloroketene and subsequent trapping of this elusive ketene with chloral.[8] However, under these conditions it was found that dichloroketene would not react with simple ketones such as acetone, cyclohexanone, and acetophenone.

In the few literature reports where ketene–carbonyl cycloadditions could produce geometrical isomers, the stereochemical course of the cycloadditions has not been reported.[7,9,10] Borrmann and Wegler, in the only report of aldoketene–carbonyl cycloadditions, described the cycloaddition of phenoxy- and ring-substituted phenoxyketenes to chloral but did not describe the stereochemistry of the products.[5]

We wish now to describe the cycloaddition of several aldoketenes with chloral and report the stereochemistry of these cycloadditions.[11] Also, we describe a method for the cycloaddition of dichloroketene with some simple ketones.

Results

The cycloaddition of aldoketenes to chloral produces *cis*- and *trans*-4-trichloromethyl-2-oxetanones.



The aldoketenes were generated *in situ* by the dehydrochlorination of the appropriately substituted acyl chlorides and/or by dehalogenation of appropriately substituted α-haloacyl halides with zinc.

As England and Krespan found in the generation of difluoroketene by *in situ* dehalogenation, the α-bromoacyl chloride is the preferred acid halide.[12] 2-Bromopropanoyl chloride consistently dehalogenated with greater ease, as evidenced by the amount of zinc consumed, than did the bromo bromide, the chloro bromide, or the chloro chloride.

The isomeric β lactones were isolated and separated by fractional distillation, preparative vpc, or column chromatography and identified by ir and nmr spectra.

(1) Support of this investigation by the Robert A. Welch Foundation, the National Science Foundation, and a North Texas State University Faculty Research Grant is gratefully acknowledged.

(2) Paper XX: W. T. Brady and J. P. Hieble, *J. Org. Chem.*, submitted for publication.

(3) H. Staudinger, *Chem. Ber.*, **41**, 1493 (1908).

(4) R. N. Lacey in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1968.

(5) F. E. Kung, U. S. Patent 2,356,459 (1944); *Chem. Abstr.*, **39**, 88 (1945).

(6) H. E. Zaugg, *Org. React.*, **8**, 314 (1954).

(7) D. Borrmann and R. Wegler, *Chem. Ber.*, **99**, 1245 (1966).

(8) D. Borrmann and R. Wegler, *ibid.*, **102**, 64 (1969).

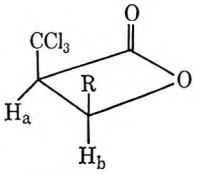
(9) D. Borrmann and R. Wegler, *ibid.*, **100**, 1575 (1967).

(10) R. H. Hasek and E. U. Elam, U. S. Patent 3,004,989 (1961); *Chem. Abstr.*, **56**, 4623 (1962).

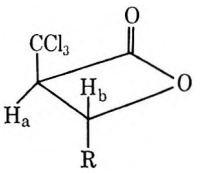
(11) A preliminary report of a portion of this work has appeared: W. T. Brady and L. Smith, *Tetrahedron Lett.*, 2963 (1970).

(12) D. C. England and C. G. Krespan, *J. Org. Chem.*, **33**, 816 (1968).

Configurational assignments were made on the basis of the nmr coupling constants of the methinyl protons.



J_{ab} (cis) = 6 cps



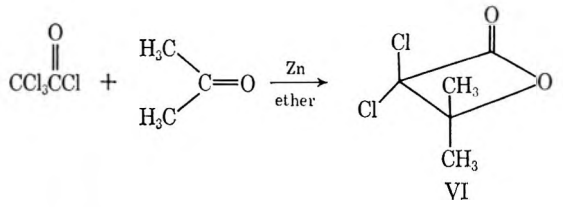
J_{ab} (trans) = 3 cps

The doublet for H_a appears downfield from the resonance of H_b by 25–75 cps.

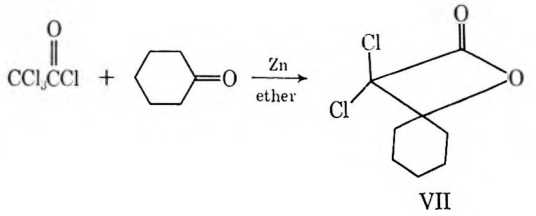
The isomer distributions were determined as ratios of integrated peak areas on gas chromatograms of the reaction solutions with the exception of the phenoxyketene–chloral system. The ratio, *cis-/trans*-IV, was obtained by nmr integration of the methinyl region.

The vpc and nmr methods were compared by making an artifical mixture of *cis-* and *trans*-3-methyl-2-oxetanone (I). The ratio, *cis-/trans*-I, in the mixture was 1.10 by weight. An average of several integrations of the *cis-* and *trans*-methinyl doublets in the nmr spectrum (30% in $CDCl_3$) of the mixture yielded *cis-/trans*-I = 1.12. The average integration of the peak areas in several chromatograms from the nmr solution yielded *cis-/trans*-I = 1.06. The experimentally determined distributions for compounds I–IV are summarized in Table I.

The increased yield in the synthesis of I by dehalogenation as opposed to dehydrochlorination may be seen in Table I. To further explore the effect of the method of ketene generation on the cycloaddition, dehalogenations of trichloroacetyl chloride in the presence of acetone and cyclohexanone were investigated and found to produce VI and VII.



VI



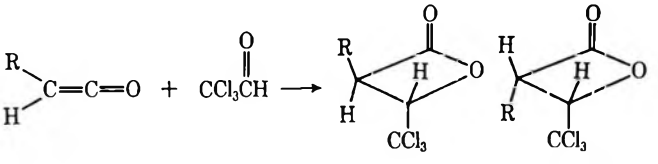
VII

As a comparison of the two methods, dimethylketene, when prepared by *in situ* dehydrochlorination of isobutyryl chloride with triethylamine in the presence of chloral, yielded 15% V. Debromination of 2-bromo-2-methylpropanoyl bromide with zinc in the presence of chloral produced 60% V.

When dimethylketene was prepared by pyrolysis of the dimer, tetramethyl-1,3-cyclobutadione, and combined with chloral in ether, V was produced in 10% yield. An identical sample containing zinc yielded 65% of V. Oshe and coworkers have reported that V is obtained in 65% yield when the cycloaddition is catalyzed by boron trifluoride etherate.[13]

TABLE I

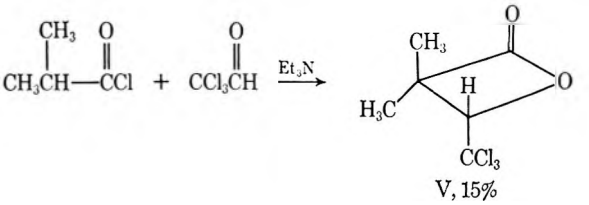
ALDOKETENE–CHLORAL CYCLOADDITIONS



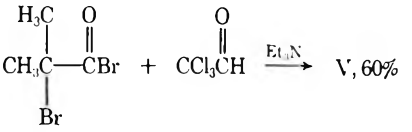
trans cis

Compd	R	Method[a]	cis/trans	Yield, %
I	CH_3	DHX	1.4	43
I	CH_3	DX	1.4–2.0	95
II	Cl	DHX	1.6	40
III	*i*-Pr	DX	0.9	25
IV	PhO	DHX	1.7	61

[a] DHX = dehydrohalogenation; DX = dehalogenation.

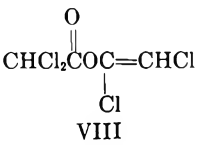


V, 15%



V, 60%

In an attempt to produce chloroketene and effect the *in situ* cycloaddition to chloral by dehalogenation, dichloroacetyl chloride and chloral were treated in the usual manner with zinc. The product isolated, however, was concluded to be α,β-dichlorovinyl dichloroacetate (VIII) from the spectral data and elemental analysis.



VIII

Diphenyl-, phenylmethyl-, phenylethyl-, and phenylketenes exhibited very little reactivity toward chloral under a wide variety of conditions.

β lactones normally eliminate carbon dioxide and produce olefins when heated.[14] However, when heated at 160° for 6–12 hr, I and II were recovered unaltered. The unusual thermal stability of 4-trichloromethyl-2-oxetanones has been reported by Ohse and coworkers for 3,3-dimethyl-4-trichloromethyl-2-oxetanone (V).[13] When heated, 3,3-dichloro-4,4-dimethyl-2-oxetanone (VI) decarboxylated in the expected manner to produce 1,1-dichloro-2-methylpropene.

Discussion

The isomer distributions obtained from the cycloaddition of several different aldoketenes with chloral

(13) H. Oshe, R. Palm, and H. Cherdron, *Monatsh. Chem.*, **98**, 2138 (1967).

(14) H. C. Gilch, *J. Org. Chem.*, **30**, 4392 (1965).

(Table I) reveal that the reaction is not stereoselective. Aldoketene–olefin cycloadditions are concerted processes and stereoselectively produce *cis*- or *endo*-cyclobutanones.[15-17] In contrast, aldoketene–imine cycloadditions occur *via* a dipolar intermediate stereoselectively to yield *trans*-2-azetidinones.[18]

That the isomer distributions for the aldoketene–chloral cycloadditions are approximately the same regardless of the nature of (a) the substituent on the ketene, (b) the reaction solvent, or (c) the method of *in situ* preparation of the ketene suggests a concerted process. The lack of reactivity of the phenylketenes was very unexpected but suggests that a dipolar intermediate is not involved since phenyl groups would be very stabilizing.

If the cycloaddition of the aldoketenes to chloral is a concerted process, the conservation of orbital symmetry considerations should predict the steric route of the cycloaddition. A consideration of the four possible orthogonal approaches leads to the conclusion that both isomers would be expected with perhaps a predominance of the cis isomer.[16]

The cycloaddition of dichloroketene with acetone and cyclohexanone when the ketene is generated *in situ* by dehalogenation suggested a catalytic effect by zinc and/or zinc halides. This was confirmed by the cycloaddition of dimethylketene with chloral in the presence and absence of activated zinc. The role of the zinc is probably activation of the carbonyl functionality since ketene–olefin cycloadditions are not catalyzed by zinc under identical conditions. Although zinc enhances the reaction of both dichloro- and methylketenes with chloral, the reactivities of dichloroketene and methylketene differ markedly. When methylketene was generated *in situ* by dehalogenation, no evidence of cycloaddition with benzaldehyde, acetone, 2-butanone, or cyclohexanone could be found.

Experimental Section

Nuclear magnetic resonance (nmr) spectra were recorded on a Jeolco Minimar 60-Mcps or Jeolco NMR PS 100-Mcps spectrometer. Mass spectra were obtained with a Hitachi RMU-6E mass spectrometer. An F & M Scientific Model 700 was used for analytical gas chromatography and an Aerograph 90A was used for small scale preparative purposes. Columns of 4, 6, and 8 ft by 0.25 in. packed with 10% SE-30 on Chromosorb W (DMSC) 60–80 mesh were used on both instruments.

All of the solvents were dried with calcium or lithium aluminum hydrides, distilled, and stored over molecular sieves, 4A, prior to use. The acid halides were prepared from the corresponding acids by classical procedures. The isolable ketenes were prepared by standard procedures found in the literature. Chloral was vacuum distilled and stored under nitrogen in brown glass bottles with septum caps at 0–5°. Portions were removed with a syringe as needed. Other aldehydes and ketones were distilled and stored in the same manner.

Activation of Zinc.—Granular zinc (15 g, 20 mesh) was rinsed in 75 ml of 5% aqueous HCl containing 0.1 g of $HgCl_2$/50 ml until the surface was bright. The zinc was separated by filtration, washed with distilled water and with acetone, and dried with a stream of nitrogen. The zinc was transferred to the reaction flask under nitrogen and covered with ether.

Cycloaddition of Methylketene and Chloral to Give 3-Methyl-4-trichloromethyl-2-oxetanone (I). Method A.—Triethylamine, 32 ml (230 mmol), in 75 ml of ether was added to a vigorously stirred solution of propionyl chloride, 20 ml (230 mmol), and chloral, 20 ml (204 mmol), in 300 ml of ether at room temperature. Filtration of the reaction mixture after 4 hr revealed a theoretical amount of salt. Concentration of the filtrate and distillation of the residue yielded a crude mixture of *cis*- and *trans*-I, 43% based on chloral. Fractional distillation gave three fractions, 51–54°, 54–55°, and 56° (0.2 mm). The first two fractions were shown to be mixtures of *cis*- and *trans*-I: ir 1870 cm^{-1} (C=O); nmr ($CDCl_3$) (*cis*-I) δ 1.55 (d), 4.2 (m), and 5.08 (d, J = 6.8 cps); nmr (*trans*-I) δ 1.55 (d), 3.81 (m), and 4.77 (d, J = 3.2 cps). Fraction three was found to be pure *cis*-I: nmr (CCl_4) δ 1.53 (d, 3 H), 4.08 (m, 1 H), and 4.98 (d, J = 6.8 cps, 1 H). Spin decoupling of the methyl resonane at δ 1.53 reduced the quintet at 4.08 to a doublet, J = 6.8 cps. Spin decoupling of the quintet reduced the methyl doublet to a singlet.

Anal. Calcd for $C_5H_5Cl_3O_2$: C, 29.52; H, 2.48. Found: C, 29.66; H, 2.46.

The *cis*-/*trans*-I in the reaction mixture was 1.39 as determined by vpc.

The dehydrochlorination of propionyl chloride in the presence of chloral was also carried out in hexane, tetrahydrofuran, and acetonitrile with approximately the same yields and isomer distributions of I.

Method B.—A solution of 2-bromopropanoyl chloride, 10 ml (98.5 mmol), in 25 ml of ether was added dropwise to rapidly stirred zinc, 12 g, in 150 ml of ether containing chloral, 15 ml (153 mmol). The reaction temperature was maintained below the boiling point of ether by cooling the reaction flask with a water bath. Filtration of the reaction mixture after 4 hr revealed that a theoretical amount of zinc had been consumed. The filtrate was concentrated and extracted with hexane. Distillation of the concentrated hexane extracts produced I in 95% yield. The isomer distribution in the reaction mixture during the reaction was 2.1 as determined by vpc.

Cycloaddition of Chloroketene and Chloral to Give 3-Chloro-4-trichloromethyl-2-oxetanone (II).—Triethylamine, 19 ml (132 mmol), in 50 ml of hexane was slowly added to a rapidly stirred solution of chloroacetyl chloride, 10 ml (132 mmol), and chloral, 15 ml 153 mmol), in 150 ml of hexane at room temperature. After the addition was complete, stirring was continued for 2 hr. Filtration resulted in a theoretical amount of salt. Concentration of the filtrate and distillation of the residue yielded (40%) a mixture of *cis*- and *trans*-II: ir 1870 cm^{-1} (C=O); nmr ($CDCl_3$) (*cis*-II) pair of doublets centered at δ 5.58 and 5.18 (J = 6.0 cps); nmr (*trans*-II) pair of doublets centered at δ 5.25 and 5.04 (J = 3.0 cps). Fractional distillation at 0.1 mm gave *trans*-II (bp 56–58°), several fractions containing both isomers, and *cis*-II (bp 78–80°): nmr (CCl_4) (*trans*-II) δ 5.44 (d, J = 3.0 cps, 1 H) and 5.17 (d, J = 6.0 cps, 1 H).

Anal. Calcd for $C_4H_2Cl_4O_2$: C, 21.46; H, 0.90. Found: C, 21.48; H, 1.02.

The *cis*-/*trans*-II in the reaction mixture was 1.64 as determined by vpc.

The dehydrochlorination of chloroacetyl chloride in the presence of chloral was also conducted in ether, tetrahydrofuran, and acetone and produced approximately the same isomer ratio. The yield in acetone was lower while the ethers produced a slightly higher yield than hexane.

Dehalogenation of Dichloroacetyl Chloride in the Presence of Chloral to Give α,β-Dichlorovinyl Dichloroacetate (VIII).—Dichloroacetyl chloride, 5 ml (52 mmol), in 10 ml of ether was added to zinc, 10 g, in 50 ml of ether containing chloral, 6 ml (61 mmol), with rapid stirring and warming with a water bath. Ir spectra of the reaction solution showed only a very low concentration of II and strong C=O absorption at 1785 cm^{-1}. Filtration revealed that less than a theoretical amount of zinc had been consumed. The filtrate was concentrated and extracted with hexane. The hexane extract was concentrated *in vacuo* and the residue distilled: yield 4.1 g (60%); bp 38–39° (0.15 mm); ir 1785 (C=O) and 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.20 (s, 1 H) and 7.56 (s, 1 H).

Anal. Calcd for $C_4H_2Cl_4O_2$: C, 21.5; H, 0.90; mol wt (theoretical), 222. Found: C, 21.53; H, 0.97; mol wt (mass spectrum), 222.

Cycloaddition of Isopropylketene and Chloral to Give 3-(2-Propyl)-4-trichloromethyl-2-oxetanone (III).—A solution of 2-bromo-3-methylbutanoyl chloride, 25 ml (215 mmol), in 50 ml of ether was added dropwise to rapidly stirred zinc, 20 g, in 300 ml of ether containing chloral, 30 ml (306 mmol). Filtration after 4 hr revealed that a theoretical amount of zinc had been

(15) W. T. Brady, E. F. Hoff, Jr., R. Roe, Jr., and F. H. Parry, III, *J. Amer. Chem. Soc.*, **91**, 5679 (1969).
(16) W. T. Brady and R. Roe, Jr., *ibid.*, **92**, 4618 (1970).
(17) T. DoMinh and O. P. Strausz, *ibid.*, **92**, 1766 (1970).
(18) J. L. Luche and H. B. Kagan, *Bull. Soc. Chim. Fr.*, **6**, 2450 (1969).

consumed. The filtrate was concentrated and extracted with hexane. The hexane was removed from the extracts *in vacuo* and the residue distilled yielding 25% III. Separation of *cis*- and *trans*-III and other components was not possible by fractional distillation. *cis*-III was obtained by preparative vpc of the crude residue from the hexane extracts: ir 1860 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.27 (t, 6 H), 2.73 (m, 1 H), 3.95 (m, 1 H), and 5.30 (d, J = 6.0 cps, 1 H).

Anal. Calcd for $C_7H_9Cl_3O_2$: C, 36.3; H, 3.92. Found: C, 36.5; H, 3.84.

trans-III was separated from the other components by elution from a 18 × 300 mm silica gel column with 70:30 cyclohexane–benzene: nmr ($CDCl_3$) δ 1.25 (d, 6 H), 2.37 (m, 1 H), 3.72 (m, 1 H), and 5.0 (d, J = 3.5 cps, 1 H).

The isomer distribution in the reaction mixture was 0.9 as determined by vpc.

Cycloaddition of Phenoxyketene and Chloral to Give 3-Phenxoy-4-trichloro-2-oxetanone (IV).—Triethylamine, 15.5 ml (110 mmol), in 25 ml of tetrahydrofuran was added dropwise to a rapidly stirred solution of phenoxyacetyl chloride, 15 ml (110 mmol), and chloral, 15 ml (153 mmol), in 200 ml of tetrahydrofuran at room temperature. After 2 hr, filtration yielded a theoretical amount of salt. Distillation of the concentrated filtrate produced two main fractions of IV (61%), bp 140 and 157° (0.2 mm). The second fraction solidified and was purified sublimation at 70° (0.05 mm), mp 70–72°. *cis*-IV: ir 1870 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.10 (d, J = 6.0 cps, 1 H), 5.62 (d, J = 6.0 cps, 1 H), and 7.2 (m, 5 H). *trans*-IV: bp 140° (0.2 mm) [lit. bp 128° (0.1 mm[7])]; nmr ($CDCl_3$) δ 5.17 (d, J = 3.0 cps, 1 H), 5.62 (d, J = 3.0 cps, 1 H), and 7.2 (m, 5 H).

The isomer distribution was determined by integration of the methinyl region of the nmr spectrum of the reaction solution. In these samples the downfield doublets of the two isomers were used since the upfield doublets of the isomers were superimposed. *cis*-/*trans*-IV = 1.7.

Cycloaddition of Dimethylketene and Chloral to Give 3,3-Dimethyl-4-trichloromethyl-2-oxetanone (V). Method A.—2-Bromo-2-methylpropanoyl bromide, 10 ml (83 mmol), in 20 ml of ether was added to rapidly stirred zinc, 15 g, in 200 ml of ether containing chloral, 15 ml (153 mmol), at room temperature. Filtration of the reaction mixture after 8 hr revealed that a theoretical amount of zinc had reacted. The filtrate was concentrated and extracted with hexane. The hexane extracts were concentrated to yield crystalline V (60%). V was further purified by sublimation at 45° (0.1 mm): mp 62–63° (lit.[13] mp 65°); nmr ($CDCl_3$) δ 1.60 (d, 6 H) and 4.74 (s, 1 H).

Method B.—Triethylamine, 13.5 ml (95.5 mmol), in 25 ml of tetrahydrofuran was added dropwise to a rapidly stirred solution of chloral, 15 ml (153 mmol), and isobutyryl chloride, 10 ml (95.5 mmol), in 200 ml of tetrahydrofuran at room temperature. The ir spectrum of the reaction solution indicated that V was formed. The yield of V was estimated to be about 15% by comparison of the gas chromatogram of the reaction solution to that of a standard solution of V. Isolation of the product was complicated by the presence of tetramethyl-1,3-cyclobutadione dimethylketene dimer.

Method C.—To 195 mmol of dimethylketene in 50 ml of ether was added 1 ml (102 mmol) of chloral. The resulting solution was transferred by a syringe to two septum bottles, one with 2 g of zinc and the other empty. After 1 hr, both solutions contained V as evidenced by vpc. During the next several hours the concentration of V, as estimated by comparison of vpc peak areas of sample and standard solutions of V, were 10 and 65% for the control and zinc sample respectively; ir (both solutions) 1850 cm^{-1} (C=O).

Cycloaddition of Dichloroketene and Acetone to Give 3,3-Dichloro-4,4-dimethyl-2-oxetanone (VI).—Trichloroacetyl chloride, 25 ml (228 mmol), in 50 ml of ether was added dropwise to rapidly stirred zinc, 18 g, in 100 ml of acetone and 500 ml of ether. The reaction temperature was maintained at 27° with a water bath. Filtration after 4 hr revealed that 86% of a theoretical amount of zinc had been consumed. The filtrate was concentrated and extracted with hexane. The hexane was removed from the extract *in vacuo*. Distillation of the residue yielded 30% of VI: bp 34° (0.5 mm); mp 24–25°; ir 1875 cm^{-1} (C=O) nmr (CCl_4) δ 1.79 (s),

Anal. Calcd for $C_5H_6Cl_2O_2$: C, 35.5; H, 3.58. Found: C, 35.7; H, 3.47.

Cycloaddition of Dichloroketene and Cyclohexanone to Give 3,3-Dichloro-1-oxaspiro[3.5]nonan-2-one (VII).—Trichloroacetyl chloride, 20 ml (182 mmol), in 50 ml of ether was added dropwise to rapidly stirred zinc, 15 g, in 200 ml of ether containing 25 ml of cyclohexanone. The reaction temperature was maintained at 30° with water bath. Filtration after 6 hr showed that 90% of the theoretical amount of zinc had been consumed. The filtrate was concentrated and extracted with hexane. Removal of the hexane and distillation of the residue afforded a 51% yield of VII: bp 62° (0.2 mm); ir 1850 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.8 (m)

Anal. Calcd for $C_8H_{10}Cl_2O_2$: C, 45.9; H, 4.82. Found: C, 45.7; H, 5.17.

Attempted Pyrolysis of *cis*-I.—A sample of *cis*-I was heated at 150° under nitrogen for 6 hr. Vacuum distillation afforded *cis*-I (90%) unchanged.

Attempted Pyrolysis of *trans*-II.—A sample of *trans*-II was heated at 160° for 12 hr. Vacuum distillation afforded *trans*-II unchanged.

Pyrolysis of VI.—A sample of VI was heated at 150° for 2 hr. Distillation yielded 50% of 1,1-dichloro-2-methylpropene, bp 106–107° (lit.[13] bp 108–110°).

Registry No.—*cis*-I, 28186-55-2; *trans*-I, 28186-56-3; *cis*-II, 28186-53-0; *trans*-II, 28186-54-1; *cis*-III, 29005-70-7; *trans*-III, 29005-71-8; *cis*-IV, 29005-72-9; *trans*-IV, 29005-73-0; V, 15347-83-8; VI, 28193-85-5; VII 29005-76-3; VIII, 29005-77-4.

The Chemistry of Pyridine. IX. Deoxydative Substitution of Pyridine *N*-Oxides by Thiophenols in the Presence of Sulfonyl Halides[1]

KENNETH F. KING[2] AND LUDWIG BAUER*

Department of Chemistry, College of Pharmacy, University of Illinois at the Medical Center, P.O. Box 6998, Chicago, Illinois 60680

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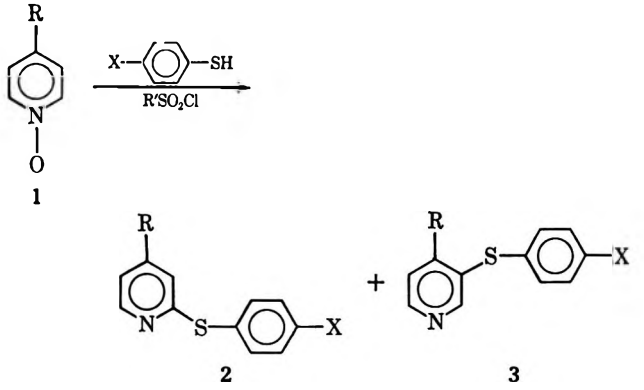
A number of pyridine and quinoline 1-oxides were substituted by thiophenols in the presence of sulfonyl chlorides in either benzene or chloroform to produce α- and β-arylthiopyridines in 30–70% yield. A considerable amount of β substitution (40–60% of total) was observed. When 2,6-lutidine 1-oxide was treated with thiophenol and benzenesulfonyl chloride in chloroform, 3- and 4-arylthio-2,6-lutidine were obtained in a ratio of 4:1. 2,4,6-Collidine 1-oxide was substituted by thiophenol to yield 3-phenylthio-2,4,6-collidine. All of the reactions are postulated to proceed *via* 1-sulfonyloxy-2-arylthio-1,2-dihydropyridine intermediates with the exception of 2,6-lutidine 1-oxide, where either a 1,2- or 1,4-dihydropyridine can be involved.

It was established that pyridine and quinoline *N*-oxides are ring substituted by mercaptans in the presence of various acid halides and anhydrides to form a mixture of 2- and 3-pyridyl and -quinolyl sulfides.[3-5] The substitution pattern and other evidence suggested that α and β substitution arose from a common 1-acyloxy-2-alkylthio-1,2-dihydropyridine intermediate.[5] Although simple mercaptans readily participated in ring substitutions when hot acetic anhydride was utilized both as acylating agent and solvent,[5] ethyl thioglycolate and thiophenols did not react. Since these thiols were acetylated quantitatively under these conditions, it appeared that their rate of attack on the activated heteroaromatic ring was too slow to compete with acylation. The electron-attracting nature of the ester in ethyl thioglycolate and that of the arene in thiophenols could decrease the nucleophilicity of these thiol groups sufficiently to contribute to this subtle difference in behavior.

To promote nucleophilic attack by these thiols on the ring, its electrophilicity would have to be enhanced. In changing the acylating agent from acetic anhydride to a sulfonyl halide, deoxydative substitution of **1** took place to form a mixture of sulfides **2** and **3** (Table I).



The reaction is attributed to attack by the thiophenol on the highly electrophilic α position of **4** to form **5**. The facile departure of sulfonate ion from **5** to form the highly energetic nitrenium–carbonium ion pair, **6**, is in concert with the ready N–O cleavage experienced by oxime, hydroxamic acid, and *O*-hydroxylamine sulfonates.[6-8] The subsequent involvement of **7** to form **3** has been discussed previously.[5] Support for the ion pair in a tight solvent cage, **6**, in these reactions emerges from the fact that, in changing from benzene to chloroform, the isomer ratio for a particular reaction remains constant (Table I).

TABLE I[a]

R in 1	X in thiophenol	R' in sulfonyl halide	Solvent[b]	Yield, %	Isomer distribution[c] 2	3	Disulfide[f] ArSSAr
H	H	CH_3	B	27.2	40	60[d]	60.2
H	H	C_6H_5	B	30.2	41	59[d]	52.8
H	H	C_6H_5	C	45.7	39	61[d]	
H	Cl	C_6H_5	C	50.0	37	63[e]	35.6
H	*tert*-C_4H_9	C_6H_5	B	33.0	32	68	30.9
H	*tert*-C_4H_9	C_6H_5	C	36.1	38	62	
CH_3	H	CH_3	B	41.0	56	44	37.4
CH_3	H	CH_3	C	62.3	54	46	19.8
CH_3	H	C_6H_5	B	33.6	67	33	51.1
CH_3	H	C_6H_5	C	72.3	66	34	21.8
CH_3	Cl	CH_3	B	49.2	46	54	27.4
CH_3	Cl	C_6H_5	C	73.2	44	56	19.3
CH_3	*tert*-C_4H_9	C_6H_5	B	40.4	38	62	43.0
CH_3	*tert*-C_4H_9	CH_3	C	55.5	27	73	
CH_3	*tert*-C_4H_9	C_6H_5	C	53.6	34	66	27.4
tert-C_4H_9	H	C_6H_5	C	25.0	57	43	
tert-C_4H_9	Cl	C_6H_5	C	26.6	49	51	
tert-C_4H_9	*tert*-C_4H_9	C_6H_5	B	34.8	37	63	60.2
tert-C_4H_9	*tert*-C_4H_9	C_6H_5	C	28.9	40	60	58.7

[a] The reactions were carried out under the following standard set of conditions: 1 equiv of the sulfonyl halide was added to a stirred equimolar mixture of the *N*-oxide and thiol in either benzene or chloroform at 0°. [b] B = benzene, C = chloroform. [c] Isomer distribution determined by pmr, except where noted. [d] Determined by gc. [e] Determined by column chromatography. [f] Not determined where space is blank.

Additional evidence for the high level of induced electrophilicity at the β position of **6** is provided from several experiments. A bulky group at the γ position offered little hindrance, since 4-*tert*-butylpyridine 1-oxide experienced a high degree of β substitution (Table I). 2,6-Lutidine 1-oxide was not ring substituted by mercaptans in acetic anhydride[5] but reacted with thiophenol and benzenesulfonyl chloride to give a mixture of 3- and 4-arylthio-2,6-lutidine in the ratio of better

(1) Taken in part from the Ph.D. dissertation of K. F. King, University of Illinois at the Medical Center, Chicago, Ill. Presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(2) National Science Foundation Trainee, 1966–1970.

(3) L. Bauer and T. Dickerhofe, *J. Org. Chem.*, **29**, 2183 (1964); *ibid.*, **31**, 939 (1966).

(4) L. Bauer and A. L. Hirsch, *ibid.*, **31**, 1210 (1966).

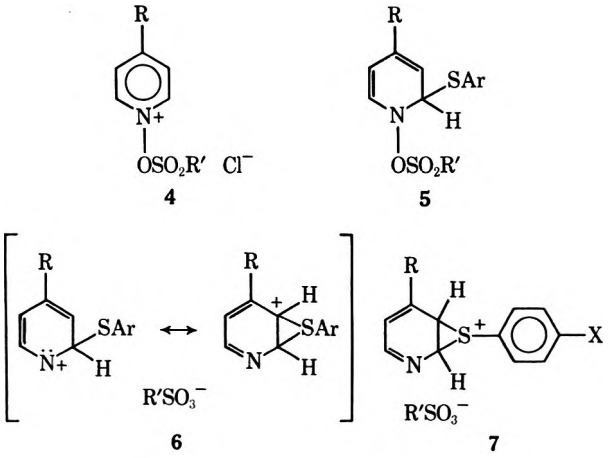
(5) F. M. Hershenson and L. Bauer, *ibid.*, **34**, 655, 660 (1969).

(6) L. G. Donaruma and W. Z. Heldt [*Org. React.*, **11**, 1 (1960)] report that the rate of rearrangement was proportional to the strength of the esterifying acid, *i.e.*, $C_6H_5SO_3H > RCO_3H$.

(7) The ease by which *O*-sulfonyl hydroxamates rearrange has been demonstrated frequently; see F. M. Hershenson, L. Bauer, and K. F. King, *J. Org. Chem.*, **33**, 253 (1968).

(8) J. P. Fleury, J. M. Biehler, and M. Desbois, *Tetrahedron Lett.*, 4091 (1969).

than 4:1. It is not surprising that the *N*-sulfonyloxy group imparted considerable electorphilic character to the γ position which provided the 4-arylthio-2,3-lutidine. An unanswered question is whether the β-substituted product is the result of sulfide migration from a 1,2- or 1,4-dihydropyridine derivative from 2,6-lutidine 1-oxide. The methyl group in the 2 position should not be able to prevent attack by thiophenol to form an intermediate analogous to **5**. Better support for attack on a carbon bearing a methyl group is advanced when it was discovered that 2,4,6-collidine 1-oxide was substituted by thiophenol in the presence of benzenesulfonyl chloride to furnish 3-phenylthio-2,4-collidine.



4 **5**

6 **7**

Change in Solvent.—Since solutions could not be maintained during each of the reactions in benzene or chloroform, few conclusions can be drawn beyond the one stated above regarding isomer distribution.

Change in Sulfonyl Halide.—These experiments indicate that a change from benzenesulfonyl to methanesulfonyl chloride resulted in a higher proportion of **3**, using similar substrates and solvents. Two effects operating in the same direction in **5** when R = CH_3 could be responsible for the relative increase of β substitution. The benzenesulfonyl derivative **5** (R = C_6H_5) imparts greater acidity to the α proton which is expected to be lost during the aromatization process. The more facile departure of benzenesulfonate to methanesulfonate ion, combined with the more acidic H-2, would favor α substitution. By the same token, scission of the methanesulfonate ion might be assisted by simultaneous migration of the sulfide in **5** to form **7** and thereby indirectly increase β substitution.

γ Substituent in 1.—Remarkable little variation was observed in β substitution as H was replaced by CH_3 and *tert*-C_4H_9, in comparable situations, which reinforces the proposed mechanism.

Para Substituent in the Thiophenol.—Although the data offer certain trends, these are interpreted with caution. For the reactions of pyridine 1-oxide with benzenesulfonyl chloride in chloroform, there appeared little change in the isomer distribution as the para substituent in the thiophenol was varied from H to Cl to *tert*-C_4H_9. Since no steric hindrance would be encountered at the γ position of pyridine 1-oxide, this would reflect few electronic effects due to the para substituent in the intermediate **7**. However, in reactions of both 4-picoline and 4-*tert*-butylpyridine 1-oxides, the percent of β isomer increased as the thiophenol X varied: *tert*-C_4H_9 > Cl > H. This could indicate that stabilization of **7** by the *tert*-butyl and chloro substituent aids its formation and leads to **3**, in the face of some steric encumberance at the γ position.

Related Reactions.—The reaction of lepidine 1-oxide with thiophenol and methanesulfonyl chloride gave a mixture of 2- and 3-phenylthiolepidines in the ratio of better than 4:1. The lesser amount of β substitution experienced in lepidine, compared to 4-picoline 1-oxide, is attributed to the inhibition of forming the equivalent structure to **7**, since in lepidine the benzenoid aromaticity would have to be disrupted.

When *tert*-butyl mercaptan was used as the thiol with 4-picoline 1-oxide and benzenesulfonyl chloride in chloroform, a poor yield of sulfides was obtained; the ratio of α to β substitution was 47:53. When these figures are compared with a ratio of 70:30 using acetic anhydride as the acylating agent,[5] they would point again to an increased electrophilicity at the β position when sulfonyl halides are employed. By contrast, ethyl thioglycolate produced only the 2-substituted sulfide. Apparently, migration was sufficiently discouraged by the lesser nucleophilicity of the sulfur nucleophile.

By-products.—In all of these reactions, the formation of a large amount of disulfides was quite apparent, but even more puzzling was the formation of a considerable quantity of the pyridine or quinoline related to the starting *N*-oxide; although no attempt was made to isolate pyridine or 4-picoline, the less water-soluble bases, like 4-*tert*-butylpyridine and lepidine, appeared as part of the distillate.[3] It seems plausible that the reduction of the *N*-oxide, and disulfide formation (at least, in part), can be linked to at least one process. Recent papers on the oxidation of thiols to disulfides by chloramine and the reactions of sulfenimides [$(RCO)_2NSR$] with thiols to form disulfides[9] suggests that sulfenamides could serve as precursors to disulfides. Such a sulfenamide could be created in our work if the sulfonate ion in **4** is displaced by ArSH to create the intermediate, R_3NSAr^+ Cl^-, and 1 mol of the sulfonic acid. A second attack by ArSH would then yield the disulfide and the pyridine (R_3N). At least this mechanism could explain the reduction of the *N*-oxide by the thiol and sulfonyl halide. It is realized, of course, that the pyridine-catalyzed reaction of thiophenol with sulfonyl halides yields disulfides directly.[10]

Experimental Section[11]

Starting Materials.—Generous gifts of the following chemicals are gratefully acknowledged: *tert*-butyl mercaptan from Pennwalt Chemical Co. and Phillips Petroleum Co.; 4-*tert*-butylpyridine, pyridine 1-oxide, 4-picoline 1-oxide, and 2,6-lutidine 1-oxides from Reilly Tar and Chemical Co. Alumina used was either Alcoa (grade F-20) or Woelm neutral (activity grade I)

(9) H. H. Sisler, N. K. Kotia, and R. E. Highsmith, *J. Org. Chem.*, **35**, 1742 (1970); K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, 3547 (1970); D. N. Harpp, *et al.*, *ibid.*, 3551 (1970).

(10) T. F. Parsons, J. D. Buckman, D. E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965).

(11) Melting and boiling points are uncorrected. Nitrogen analyses were obtained by one of us (K. F. K.) using a Coleman nitrogen analyzer, Model 29. Pmr spectra were taken at 60 MHz using a Varian A-60 spectrometer. Signals are reported in parts per million (δ) downfield from internal tetramethylsilane (TMS). Each A-60 spectrum was calibrated by a sample of TMS (δ 0.0 in $CHCl_3$ δ 7.28). Proton assignments were based on correct integral information, on chemical shifts anticipated for the particular protons, and, whenever possible, spin–spin coupling constants (J) derived from first-order analysis. Only pertient pmr parameters are reported. All compounds gave appropriate parent ions in their mass spectra at 70 eV using a Hitachi Perkin-Elmer RMU-6D mass spectrometer equipped with a Honeywell Visicorder.

activated at 120° for 15 hr. Benzene was thiophene free and petroleum ether was the fraction of bp 30–60°. Thin layer chromatographs (tlc) were determined on silica gel with a fluorescent indicator (Eastman chromagram sheet 6060) using benzene–chloroform (1:1) as the developer. The spots were detected by uv light or iodine stains.

Gas chromatography (gc) was performed using a Varian Aero-Prep 700. Two columns were used. For the arylthiopyridines a diethylene glycol succinate column (5%) on Chromosorb G was used isothermally (180°). All other separations were effected utilizing SE-30 on Chromosorb W (20%) with the injection temperature reported and a power regulator setting of "50." Although determination of isomer ratios on the 5% DEGS column was not always possible because of broad peaks, a fraction often eluting over a period of 0.5 hr yielded pure samples for analytical purposes.

General Procedure B. Reaction of Pyridine 1-Oxide and Thiophenol with Benzenesulfonyl Chloride in Benzene.—To a vigorously stirred solution of pyridine 1-oxide (9.5 g, 0.1 mol) in benzene (100 ml) and thiophenol (11.02 g, 0.1 mol) in an ice water bath (4°) was added benzenesulfonyl chloride (17.66 g, 0.1 mol) in one portion. The temperature rose sharply to 31° and a fine precipitate appeared. The mixture was stirred in the ice bath for 0.5 hr and then washed with 5% NaOH (two 50-ml portions). The basic phase was back-extracted with benzene (two 30-ml portions) and the aqueous phase was not examined further. The combined benzene fractions were extracted with dilute HCl (1:3, three 50-ml portions). The acid extract was made basic (pH 10) with 50% NaOH and extracted with chloroform (three 50-ml portions). Distillation afforded 5.67 g, bp 107–109° (0.14 Torr). By means of gc the following compounds were collected (injection temperature 180°). **3-Phenylthiopyridine** [59%, retention time(rt) 121.2 min]: pmr ($CDCl_3$) δ 8.71 (H-2), 8.57 (H-6), 7.68 (H-4), 7.23 (H-5) ($J_{2,4} = J_{2,5} = 0.9$, $J_{4,5} = 7.9$, $J_{5,6} = 4.5$ Hz). *Anal.* Calcd for $C_{11}H_9NS$: N, 7.48. Found: N, 7.39. **2-Phenylthiopyridine** (41%, rt 140.6 min): pmr ($CDCl_3$) δ 8.55 (H-6), 7.35–7.80 (m, H-4 and phenyl protons), 6.86–7.20 (m, H-3, H-5) ($J_{3,6} = 1.1$, $J_{4,6} = 2.1$, $J_{5,6} = 4.5$ Hz). *Anal.* Calcd for $C_{11}H_9NS$: N, 7.48. Found: N, 7.54. This sulfide was described previously [lit.[12] bp 160–162° (8 Torr)].

Fom the benzene solution above was isolated phenyl disulfide (5.76 g, 52.8%), mp 54–56° (lit.[13] mp 60°). All other reactions performed in benzene were carried out similarly and the yields and isomer distribution recorded in Table I.

General Procedure C. With Benzenesulfonyl Chloride in Chloroform.—The reaction was carried out on the same scale as described for procedure B with chloroform (100 ml) as solvent. A minor modification in the work-up was essential since some arylthiopyridine hydrochlorides possessed appreciable solubility in chloroform and could not be extracted with dilute hydrochloric acid. After 0.5 hr, the mixture was extracted with 5% NaOH and the chloroform removed *in vacuo* and replaced by benzene (100 ml). The products were isolated as under procedure B and the results listed in Table I.

Reaction of Pyridine 1-Oxide and *p*-Chlorothiophenol.—The arylthiopyridines were distilled, bp 135–137° (0.15 Torr), and separated on alumina. **2-*p*-Chlorophenylthiopyridine**[14] (R_f 0.48) was eluted by petroleum ether: pmr ($CDCl_3$) δ 8.50 (H-6) ($J_{3,6} = 1.3$, $J_{4,6} = 1.9$, $J_{5,6} = 4.6$ Hz). *Anal.* Calcd for $C_{11}H_8ClNS$: N, 6.32. Found: N, 6.37. **3-*p*-Chlorophenylthiopyridine** (R_f 0.32) was eluted by benzene: pmr ($CDCl_3$) δ 8.81 (H-2), 8.71 (H-6) ($J_{2,4} = 2.4$, $J_{2,5} = 0.9$, $J_{4,6} = 1.7$, $J_{5,6} = 4.1$ Hz). *Anal.* Calcd for $C_{11}H_8ClNS$: N, 6.32. Found: N, 6.25.

p-Chlorophenyl disulfide was recrystallized from 95% ethanol, mp 68–70° (lit.[15] mp 72–74°).

Reaction of Pyridine 1-Oxide and *p*-*tert*-Butylthiophenol.—The sulfides were collected, bp 145–147° (0.10 Torr), and separated by gc (injection temperature 180°). **3-*p*-*tert*-Butylphenylthiopyridine** (rt 232.0 min): pmr ($CDCl_3$) δ 8.63 (H-2), 8.55 (H-6), 1.31 (*tert*-C_4H_9) ($J_{2,4} = 2.2$, $J_{2,5} = 0.8$, $J_{4,6} = 1.8$, $J_{5,6} = 4.8$ Hz). *Anal.* Calcd for $C_{15}H_{17}NS$: N, 5.76. Found: N, 5.68. **2-*p*-*tert*-Butylphenylthiopyridine** (rt 272.5 min): pmr ($CDCl_3$) δ 8.55 (H-6), 1.33 (*tert*-C_4H_9) ($J_{3,6} = 1.1$, $J_{4,6} = 1.9$, $J_{5,6} = 4.7$ Hz). *Anal.* Calcd for $C_{15}H_{17}NS$: N, 5.76. Found: N, 5.68.

The isomer distribution was checked by estimating the ratio of the *tert*-butyl signals (at 50-Hz sweep width). Because the peaks are singlets with no coupling and because of their close chemical shifts, peak height rather than integrated area was determined to be most accurate.

The original basic aqueous solution was extracted continuously (18 hr) with CH_2Cl_2. Distillation yielded pyridine 1-oxide 3.47 g, bp 104–105° (0.05 Torr), identified by its ir.

p-*tert*-Butylphenyl disulfide was recrystallized from 95% ethanol, mp 84–86° (lit.[16] mp 88.5–89°).

Reaction of 4-Picoline 1-Oxide and Thiophenol.—The arylthiopyridines boiled between 114 and 116° (0.15 Torr) and were separated by gc (injection temperature 180°). **3-Phenylthio-4-picoline** (rt 114.4 min): pmr ($CDCl_3$) δ 8.62 (H-2), 8.52 (H-6), 2.37 (CH_3) ($J_{5,6} = 4.8$ Hz). *Anal.* Calcd for $C_{12}H_{11}NS$: N, 6.96. Found: N, 6.85. **2-Phenylthio-4-picoline**[17] (rt 155.3 min): pmr ($CDCl_3$) δ 8.42 (H-6), 2.21 (CH_3) ($J_{3,6} = 0.8$, $J_{5,6} = 4.8$ Hz). *Anal.* Calcd for $C_{12}H_{11}NS$: N, 6.96. Found: N, 6.82.

The isomer distribution was checked by integration of the methyl signals at δ 2.37 and 2.21.

Reaction of 4-Picoline 1-Oxide and *p*-Chlorothiophenol.—The arylthiopyridines were collected, bp 124–126° (0.15 Torr), and separated on alumina. **2-*p*-Chlorophenylthio-4-picoline** was eluted by benzene (R_f 0.38): pmr ($CDCl_3$) δ 8.42 (H-6), 6.94 (H-5), 6.90 (H-3), 2.24 (CH_3) ($J_{3,6} = 1.1$, $J_{5,6} = 4.4$ Hz). *Anal.* Calcd for $C_{12}H_{10}ClNS$: N, 5.94. Found: N, 5.83. **3-*p*-Chlorophenylthio-4-picoline** (R_f 0.22) was eluted in later fractions by benzene: pmr ($CDCl_3$) δ 8.62 (H-2), 8.54 (H-6), 2.34 (CH_3) ($J_{5,6} = 5.1$ Hz). *Anal.* Calcd for $C_{12}H_{10}ClNS$: N, 5.94. Found: N, 5.90.

Reaction of 4-Picoline 1-Oxide and *p*-*tert*-Butylthiophenol.—The sulfides were distilled, bp 160–162° (0.2 Torr), and separated on alumina. **2-*p*-*tert*-Butylphenylthio-4-picoline** (R_f 0.25) was eluted by petroleum ether–benzene (1:1): pmr ($CDCl_3$) δ 8.31 (H-6), 6.82 (H-3), 6.34 (H-5), 2.16 (CH_3), 1.31 (*tert*-C_4H_9); (C_6D_6) 8.26 (H-6), 7.47 (4-Ar H), 6.83 (H-3), 6.34 (H-5), 1.62 (CH_3), 1.14 (*tert*-C_4H_9) ($J_{3,5} = 1.4$, $J_{3,6} = 0.8$ $J_{5,6} = 4.9$, $J_{5,CH_3} = 0.8$, $J_{3,CH_3} = 0.8$ Hz). A large shift (0.54 ppm) of the picoline methyl signal was observed when C_6D_6 was the solvent. A change to this solvent aided the determination of the isomer ratio. *Anal.* Calcd for $C_{15}H_{19}NS$: N, 5.44. Found: N, 5.50. **3-*p*-*tert*-Butylphenylthio-4-picoline** (R_f 0.145) was eluted with benzene: pmr ($CDCl_3$) δ 8.48 (H-2), 8.42 (H-6), 7.15 (H-5), 2.33 (CH_3), 1.27 (*tert*-C_4H_9); pmr (C_6D_6) 8.79 (H-2), 8.42 (H-6), 7.15 (4-Ar H), 6.64 (H-5), 2.08 (CH_3), 1.10 (*tert*-C_4H_9) ($J_{2,5} = 0.9$, $J_{5,6} = 4.8$, $J_{5,CH_3} = 0.6$ Hz). *Anal.* Calcd for $C_{16}H_{19}NS$: N, 5.44. Found: N, 5.38.

The aqueous basic layer from a reaction with benzenesulfonyl chloride in benzene was extracted (24 hr) with CH_2Cl_2. Solvents were removed and the residue chromatographed on alumina. Elution with $CHCl_3$ furnished 4-picoline 1-oxide (4.36 g, mp 180–183°).

Reaction of 4-*tert*-Butylpyridine 1-Oxide and Thiophenol.—Distillation of the products using benzenesulfonyl chloride in chloroform yielded 4-*tert*-butylpyridine (0.22 g, 3.26%, ir identical with that of the authentic sample) and a mixture of the arylthiopyridines and 4-*tert*-butylpyridine 1-oxide [6.07 g, bp 126–128° (0.14 Torr)]. The 4-*tert*-butylpyridine 1-oxide in the mixture was identified by tlc comparison with an authentic sample and its pmr [δ 1.33 (*tert*-C_4H_9), 8.28 (H-2, H-6)]. The mixture was separated on alumina. **2-Phenylthio-4-*tert*-butylpyridine** (R_f 0.52) was eluted by petroleum ether–benzene (1:1): pmr ($CDCl_3$) δ 8.51 (H-6), 1.16 (*tert*-C_4H_9) ($J_{3,6} = 2.1$, $J_{5,6} = 4.0$ Hz). *Anal.* Calcd for $C_{15}H_{17}NS$: N, 5.76. Found: N, 5.68. **3-Phenylthio-4-*tert*-butylpyridine** (R_f 0.36) was eluted by ether: pmr ($CDCl_3$) δ 8.55 (H-2), 8.50 (H-6), 1.50 (*tert*-C_4H_9) ($J_{5,6} = 5.4$ Hz). *Anal.* Calcd for $C_{15}H_{17}NS$: N, 5.76. Found: N, 5.82.

Isomer distribution and yield was determined by pmr. The peaks at δ 1.16 and 1.50 (*tert*-butyl signals) provided the isomer distribution and the one at δ 1.33 gave an estimate of the amount of 4-*tert*-butylpyridine 1-oxide.

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Reaction of 4-*tert*-Butylpyridine 1-Oxide and *p*-Chlorothiophenol.—Distillation of the basic fraction yielded 4-*tert*-butylpyridine [bp 44–46° (0.15 Torr)] and a mixture of the arylthiopyridines and 4-*tert*-butylpyridine 1-oxide [bp 149–151° (0.15 Torr)].

2-*p*-Chlorophenylthio-4-*tert*-butylpyridine (R_f 0.53) was eluted from alumina by petroleum ether–benzene (1:1): pmr ($CDCl_3$) δ 8.52 (H-6), 1.23 (*tert*-C_4H_9) ($J_{3,6}$ = 1.6, $J_{5,6}$ = 4.8 Hz). *Anal.* Calcd for $C_{15}H_{16}ClNS$: N, 5.04. Found: N, 4.98. **3-*p*-Chlorophenylthio-4-*tert*-butylpyridine** (R_f 0.35) was eluted by ether: pmr ($CDCl_3$) δ 8.63 (H-6), 8.59 (H-2), 1.50 (*tert*-C_4H_9) ($J_{5,6}$ = 4.4 Hz). *Anal.* Calcd for $C_{15}H_{16}ClNS$: N, 5.04. Found: N, 5.02.

Reaction of 4-*tert*-Butylpyridine 1-Oxide and *p*-*tert*-Butylthiophenol with Benzenesulfonyl Chloride (Method B).—A modification was required in the work-up since the sulfides could not be extracted from the benzene layer by 1:3 HCl. The benzene solution contained the sulfides and *p*-*tert*-butylphenyl disulfide in the ratio of 60.9 to 39.1 (pmr). Separation was achieved most satisfactorily on alumina. Petroleum ether eluted the disulfide, followed by **2-*p*-*tert*-butylphenylthio-4-*tert*-butylpyridine**, which was eluted by petroleum ether–benzene (1:1): bp 175–180° (0.2 Torr); pmr ($CDCl_3$) δ 8.40 (H-6), 7.52 (4-phenyl H), 7.00 (H-3 and H-5), 1.33 (pyridyl *tert*-C_4H_9), 1.17 (phenyl *tert*-C_4H_9); pmr (C_6D_6) δ 8.25 (H-6), 7.47 (4 phenyl H), 7.07 (H-3), 6.70 (H-5), 1.18 (pyridyl *tert*-C_4H_9), 0.98 (phenyl *tert*-C_4H_9) ($J_{3,5}$ = 1.8, $J_{3,6}$ = 0.7, $J_{5,6}$ = 5.1 Hz). *Anal.* Calcd for $C_{19}H_{25}NS$: N, 4.68. Found: N, 4.61.

3-*p*-*tert*-Butylphenylthio-4-*tert*-butylpyridine was eluted with ether: bp 175–180° (0.2 Torr); pmr ($CDCl_3$) δ 8.47 (H-2), 8.40 (H-6), 7.30 (H-5), 1.52 (pyridyl *tert*-C_4H_9), 1.27 (phenyl *tert*-C_4H_9); pmr (C_6D_6) δ 8.80 (H-2), 8.43 (H-6), 7.04 (H-5), 1.41 (pyridyl *tert*-C_4H_9), 1.14 (phenyl *tert*-C_4H_9) ($J_{5,6}$ = 5.1 Hz). *Anal.* Calcd for $C_{19}H_{25}NS$: N, 4.68. Found: N, 4.69.

Reaction of 3,5-Lutidine 1-Oxide and *p*-*tert*-Butylthiophenol with Benzenesulfonyl Chloride (Method C).—Distillation of the basic fraction [bp 160–165° (0.45 Torr)] yielded **2-*p*-*tert*-butylphenylthio-3,5-lutidine** (5.67 g, 24.4%): pmr ($CDCl_3$) δ 8.23 (m, H-6), 7.30 (m, H-4), 2.32 (3-CH_3), 2.20 (5-CH_3), 1.29 (*tert*-C_4H_9). *Anal.* Calcd for $C_{17}H_{21}NS$: N, 5.16. Found: N, 5.06.

The benzene solution was evaporated *in vacuo* and the residue recrystallized from 95% ethanol to give the disulfide (10.17 g, 61.5%).

Reaction of 2,6-Lutidine 1-Oxide and Thiophenol with Benzenesulfonyl Chloride (Method C).—Distillation of the basic fraction yielded 2,6-lutidine 1-oxide, 2.61 g [bp 75–76° (0.15 Torr)], and the sulfides, 7.74 g [bp 109–112° (0.15 Torr)]. Elution from Woelm alumina by petroleum ether furnished **3-phenylthio-2,6-lutidine** (R_f 0.35): pmr ($CDCl_3$) δ 7.58 (H-4), 7.01 (H-5), 2.63 (6-CH_3), 2.53 (2-CH_3) ($J_{4,5}$ = 8.2 Hz). *Anal.* Calcd for $C_{13}H_{13}NS$: N, 6.51. Found: N, 6.50. Subsequent elution by ether afforded **4-phenylthio-2,6-lutidine** (R_f 0.20): pmr ($CDCl_3$) δ 6.81 (H-3, H-5), 2.45 (2-, 6-CH_3). *Anal.* Calcd for $C_{13}H_{13}NS$: N, 6.51. Found: N, 6.45. Integration of the CH_3 peaks at δ 2.53, 2.63, and 2.45 on the 50-Hz sweep-width indicated the isomer distribution to be 82% of the 3 isomer and 18% of the 4 isomer, in 36% yield, based on the *N*-oxide.

From the benzene layer was isolated phenyl disulfide (6.20 g, 56.8%).

Reaction of 2,6-Lutidine 1-Oxide and *p*-*tert*-Butylthiophenol with Benzenesulfonyl Chloride (Method C).—Distillation of the basic fraction yielded the starting *N*-oxide, 5.98 g [bp 80–83° (0.80 Torr)], and the sulfides, 3.50 g (11.7%) [bp 152–154° (0.40 Torr)]. **3-*p*-*tert*-Butylphenylthio-2,6-lutidine** was eluted from alumina by petroleum ether–benzene (1:1): pmr ($CDCl_3$) δ 7.56 (H-4), 7.42 (m, 4-Ar H), 7.04 (H-5), 2.66 (6-CH_3), 2.55 (2-CH_3), 1.30 (*tert*-C_4H_9) ($J_{4,5}$ = 8.2 Hz). *Anal.* Calcd for $C_{17}H_{21}NS$: N, 5.16. Found: N, 5.09.

Further elution with the same solvent afforded pure **4-*p*-*tert*-butylphenylthio-2,6-lutidine**: pmr ($CDCl_3$) δ 7.62 (m, 4-Ar H), 6.83 (H-3, H-5), 2.45 (2-, 6-CH_3), 1.36 (*tert*-C_4H_9). *Anal.* Calcd for $C_{17}H_{21}NS$: N, 5.16. Found: N, 5.11. Based on the *N*-oxide the yield of sulfides was 11.7% with the ratio of 3 to 4 isomers being 83:17. The disulfide was also isolated in 82% yield.

Reaction of 2,4,6-Collidine 1-Oxide and Thiophenol with Benzenesulfonyl Chloride (Method C).—Distillation of the basic fraction yielded the starting oxide, 6.55 g, 47% recovery [bp 96–99° (0.15 Torr)], and **3-phenylthio-2,4,6-collidine** [5.0 g, 9.5%, bp 127–129° (0.15 Torr)], which was purified conveniently by passing through alumina in petroleum ether: pmr ($CDCl_3$) δ 7.00–7.87 (m, 5-Ar H, H-5), 2.71 (2-CH_3), 2.57 (6-CH_3), 2.41 (4-CH_3). *Anal.* Calcd for $C_{14}H_{15}NS$: N, 6.11. Found: N, 6.21.

Reaction of Lepidine 1-Oxide and Thiophenol with Methanesulfonyl Chloride (Method B).—Distillation of the basic fraction yielded lepidine [1.88 g, bp 80–82° (0.25 Torr)] and the sulfides [12.87 g, 51.3%, bp 162–164° (0.20 Torr)]. Elution from alumina by petroleum ether–benzene (1:1) furnished **2-phenylthiolepidine**: pmr ($CDCl_3$) δ 7.25–8.08 (m, 9-Ar H), 6.85 (CH_3) (J_{3,CH_3} = 0.9 Hz). *Anal.* Calcd for $C_{16}H_{13}NS$: N, 5.57. Found: N, 5.50. Elution with benzene–ether (1:1) afforded **3-phenylthiolepidine**: pmr ($CDCl_3$) δ 8.88 (H-2), 7.60–8.31 (4-quinolyl H), 7.21 (s, 5-Ar H), 2.79 (CH_3). *Anal.* Calcd for $C_{16}H_{13}NS$: N, 5.57. Found: N, 5.47. The distribution (pmr) was 83:17 for 2 and 3 isomers.

The remaining benzene layer was evaporated *in vacuo* and the residue recrystallized from 95% ethanol to give phenyl disulfide (3.84 g, 35.2%).

Based on these results the yield of the arylthiolepidines was 51.3%.

Reaction of Pyridine 1-Oxide and Ethyl Thioglycolate with Benzenesulfonyl Chloride (Method C).—To a stirred ice-cold solution of methanesulfonyl chloride (50 ml) and pyridine 1-oxide (9.5 g, 0.1 mol) was added ethyl thioglycolate (24 g, 1.0 mol). The temperature rose sharply to 90° and remained there for 5 min and then fell slowly to 40°. A low-boiling fraction was removed [68.6 g, bp 28–31° (0.2 Torr)] and was not examined further. Its pmr spectra showed no aromatic signals. The semisolid residue was worked up for the basic fraction. Purification of the fraction by means of gc (SE-30 column, injection temperature 70°) afforded **ethyl (2-pyridinethio)acetate** (14.2% based on *N*-oxide, rt 82.0 min): bp 92–96° (0.1 Torr); pmr ($CDCl_3$) δ 1.23 (t, CH_3), 3.90 (s, CH_2), 4.13 (q, CH_2), 8.38 (H-6) ($J_{3,6}$ = 1.0, $J_{4,6}$ = 1.8, $J_{5,6}$ = 4.8 Hz); mass spectral parent peak (70 eV) at *m/e* 197. *Anal.* Calcd for $C_9H_{11}NO_2S$: N, 7.10. Found: N, 7.07.

Reaction of 4-Picoline 1-Oxide and Ethyl Thioglycolate with Benzenesulfonyl Chloride (Method C).—Work-up in the usual manner provided **ethyl (4-methyl-2-pyridinethio)acetate** [0.95 g, bp 109–111° (0.1 Torr)] which was purified on a column of alumina (eluted by petroleum ether–benzene, 1:1): pmr ($CDCl_3$) δ 8.27 (H-6), 7.08 (H-3), 6.81 (H-5), 4.11 (q, CH_2), 3.93 (s, CH_2), 2.21 (s, CH_3), 1.18 (t, CH_3) ($J_{5,6}$ = 5.1 Hz). *Anal.* Calcd for $C_{10}H_{13}NO_2S$: N, 6.63. Found: N, 6.56.

Registry No.—2 (R = H; X = H), 3111-54-4; 2 (R = H; X = Cl), 28856-69-1; 2 (R = H; X = *tert*-C_4H_9), 28856-70-4; 2 (R = CH_3; X = H), 2732-48-1; 2 (R = CH_3; X = Cl), 28856-72-6; 2 (R = CH_3; X = *tert*-C_4H_9), 28856-73-7; 2 (R = *tert*-C_4H_9; X = H), 28856-74-8; 2 (R = *tert*-C_4H_9; X = Cl), 28856-75-9; 2 (R = *tert*-C_4H_9; X = *tert*-C_4H_9), 28856-76-0; 3 (R = H; X = H), 28856-77-1; 3 (R = H; X = Cl), 28856-78-2; 3 (R = H; X = *tert*-C_4H_9), 28856-79-3; 3 (R = CH_3; X = H), 28856-80-6; 3 (R = CH_3; X = Cl), 28856-81-7; 3 (R = CH_3; X = *tert*-C_4H_9), 28856-82-8; 3 (R = *tert*-C_4H_9; X = H), 28856-83-9; 3 (R = *tert*-C_4H_9; X = Cl), 28856-84-0; 3 (R = *tert*-C_4H_9; X = *tert*-C_4H_9), 28856-85-1; 2-*p*-*tert*-butylphenylthio-3,5-lutidine, 28957-70-2; 3-phenylthio-2,6-lutidine, 28856-86-2; 4-phenylthio-2,6-lutidine, 28856-87-3; 3-*p*-*tert*-butylphenylthio-2,6-lutidine, 28856-88-4; 4-*p*-*tert*-butylphenylthio-2,6-lutidine, 28856-89-5; 3-phenylthio-2,4,6-collidine, 28957-71-3; 2-phenylthiolepidine, 5460-87-2; 3-phenylthiolepidine, 28856-91-9; ethyl (2-pyridinethio)acetate, 28856-92-0; ethyl (4-methyl-2-pyridinethio)acetate, 28856-93-1.

The Synthesis, Oxidation, and Electronic Spectra of Four Dithienothiophenes

FEIKE DE JONG AND MATTHIJS J. JANSSEN*

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

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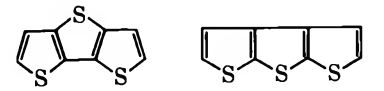
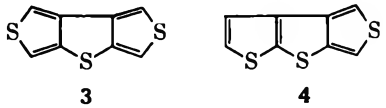
The dithienothiophenes (2–4) have been synthesized using oxidative ring closure of the appropriate dilithiodithienyl sulfides. The dilithio intermediates were obtained from α,α'-dibromodithienyl sulfides by halogen–metal interconversion. A new method is reported for the synthesis of symmetric dithienyl sulfides, consisting of the reaction of thienyllithium with bis(phenylsulfonyl) sulfide (6). Peracid oxidized the sulfur atom of the central ring exclusively. The ultraviolet spectra of the title compounds are in excellent agreement with those calculated by SCF-MO methods.

Synthesis.—Investigations of condensed thiophene systems have mainly been limited to the thienothiophene isomers.[1-3] Of the next higher homolog, dithienothiophenes, two of the six isomers (1 and 2) have been prepared,[4,5] but no spectroscopic data were reported. In view of the current interest in physical and chemical properties of condensed thiophene systems, a convenient synthesis of four dithienothiophenes (1–4), including two new ones, is described.



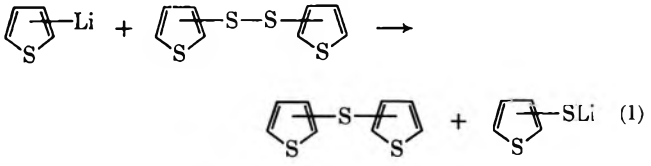
1 2



3 4

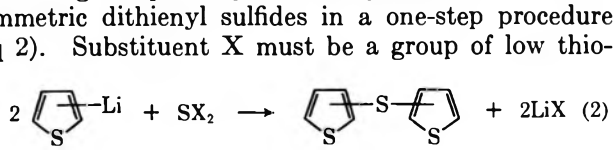
In the procedure used, α,α'-dibromodithienyl sulfides were key compounds for the ring closure. The synthesis of dithienyl sulfides from a thiophene thiol and a thienyl halide[6] cannot be used starting from bromo-substituted thiophene thiols, since treatment of 4-bromo-3-thiophene thiol with an equivalent amount of 3,4-dibromothiophene yielded only a dithieno-*p*-dithiin[7] rather than the expected 4,4′-dibromo-3,3′-dithienyl sulfide.

The reaction of thienyllithium with a dithienyl disulfide,[4,8] as represented by eq 1, was used for the synthesis



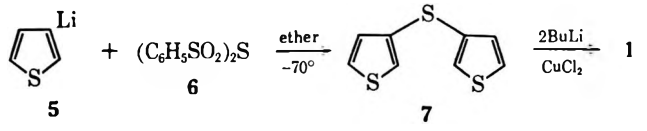
(1)

of asymmetric dithienyl sulfides. We have made use of the strong thiophilicity[9] of thienyllithium to prepare symmetric dithienyl sulfides in a one-step procedure (eq 2). Substituent X must be a group of low thiophilicity. Attempts with SCl_2 or S_2Cl_2 (X = Cl) gave only low (10–25%) yields of dithienyl sulfides, thiophene thiol being the main product isolated. Much better results (60–70% yields) were obtained from the reaction of thienyllithium with bis(phenylsulfonyl) sulfide (6) (X = $C_6H_5SO_2$). Bis(phenylsulfonyl) sulfide is easily prepared by a modification of the literature procedure.[10]



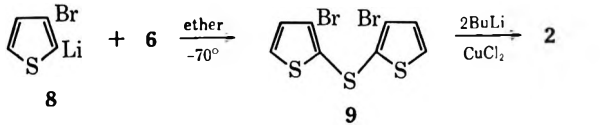
(2)

From 3-thienyllithium[11] (5) and bis(phenylsulfonyl) sulfide (6), 3,3′-dithienyl sulfide (7) was isolated in 68% yield. Dilithiation of 7 followed by oxidative ring closure by the method of Federov and Stoyanovich[4] afforded dithieno[3,2-*b*:2′,3′-*d*]thiophene (1) in 52% yield.

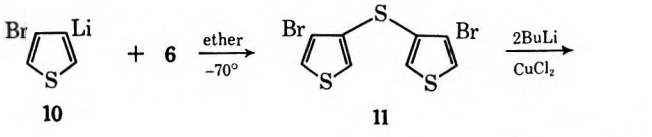


5 6 7

From 3-bromo-2-thienyllithium[11] (8), 3,3′-dibromo-2,2′-dithienyl sulfide (9) was obtained and converted to dithieno[2,3-*b*:3′,2′-*d*]thiophene (2) in 21% overall yield. This procedure is much easier to perform and gives greatly improved yields over those reported by Pandya and Tilak.[5] The previously unknown dithieno[3,4-*b*:3′4′-*d*]thiophene (3) was prepared in 20% overall yield from 4-bromo-3-thienyllithium[11] (10) *via* 4,4′-dibromo-3,3′-dithienyl sulfide (11). Alternatively,



8 9 2



10 11 3

sulfide 11 could be obtained in 83% yield from the reaction of 4-bromo-3-thienyllithium (10) and 4,4′-dibromo-3,3′-dithienyl disulfide (12). The disulfide 12 was prepared by oxidation of 4-bromo-3-thiophene thiol[12] in aqueous $K_3Fe(CN)_6$ (90%).

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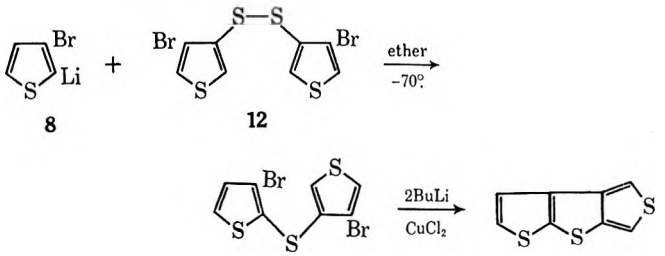
The sulfides **9** and **11** were characterized by elementary analysis, and the nmr spectra show the characteristic coupling constants for 2,3- and 2,5-substituted thiophenes.[13] The nmr spectrum of **3** in deuteriochloroform showed two doublets at δ 7.00 and 7.43 with J = 2.6 Hz. The unusually small value[14] of $J_{2,5}$ is probably due to geometrical deformation of the thiophene ring system caused by 3,4 anellation, since in systems like thieno[3,4-*b*]thiophene,[1] cyclopentadithiophenes,[15] and cyclopentadithiophenones[16] small values (1.9–2.2 Hz) for $J_{2,5}$ are also observed.

Finally, reaction of 3-bromo-2-thienyllithium[11] (**8**) and the disulfide **12** afforded 94% of 3,4′-dibromo-2,3′-dithienyl sulfide (**13**). On oxidative ring closure of the

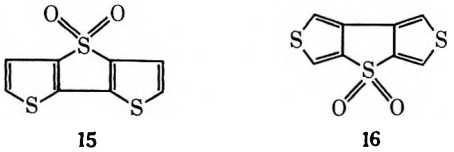


8 12 13 4

dilithio intermediate, sulfide **13** furnished dithieno[2,3-*b*:3′,4′-*d*]thiophene (**4**) in 29% yield. Its nmr spectrum shows one AB system with J = 5.5 Hz (2,3 coupling) and one with J = 2.6 Hz (2,5 coupling, but again smaller than usual).

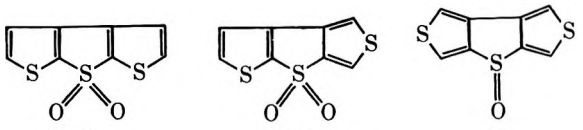
The two remaining dithienothiophenes cannot be prepared by the same procedure, owing to the inaccessibility of 2-bromo-3-thienyllithium. An alternative synthesis is being studied.

Oxidation of the Dithienothiophenes.—In order to obtain information about the relative reactivity of the three sulfur atoms in each isomer, the dithienothiophenes were subjected to peracid oxidation. When the compounds **1** and **3** were treated in acetic acid solution by hydrogen peroxide, the corresponding sulfones **15** and **16** were obtained in good yield. The presence of the sulfone group was concluded from the ir spectra, showing the characteristic sulfone absorptions at 1130 and 1290 cm^{-1}. In addition, the nmr spectra show two different protons (two doublets with J = 5.0 Hz for **15** and J = 2.4 Hz for **16**), indicating that the sulfur atom of the central ring has been oxidized.



15 16

When the dithienothiophenes **2** and **4** were treated under the same conditions with hydrogen peroxide, low yields of impure sulfones **17** and **18** were obtained. However, the latter were obtained in good yield when **2** and **4** were oxidized by *m*-chloroperbenzoic acid in dichloromethane solution at −10°. The presence of the sulfone group was again based on the ir spectra (sulfonyl absorptions at 1150 and 1300 cm^{-1}). The nmr spectrum of **17** showed the correct symmetry (two doublets with J = 5.0 Hz) expected from oxidation of the central ring.



17 18 19

The site of oxidation in **18** could be determined from its nmr spectrum showing two sets of doublets: δ 7.68, 8.15 with J = 2.4 Hz; and δ 7.80, 7.62 with J = 5.0 Hz. Formally, the structures obtained by oxidation of one of the terminal rings would give rise to a similar splitting pattern. However, no change in coupling constants is observed upon going from the starting dithienothiophene **4** to the oxidized product **18**, indicating that the aromaticity of the thiophene rings is not drastically changed.[17] From these considerations and by anology with the oxidation products of the other dithienothiophene isomers, structure **18** is assigned to this sulfone.

Although the presence of the intermediate sulfoxides could be demonstrated by tlc, only in the case of dithieno[3,4-*b*:3′,4′-*d*]thiophene (**3**) the sulfoxide **19** was isolated free from the sulfone. The structure of **19** was supported by its elementary analysis and its ir spectrum showing the characteristic sulfoxide absorption at 1030 cm^{-1}.

Electronic Spectra.—In order to correlate chemical and physical properties of the dithienothiophenes with their structures, we carried out LCI–SCF–MO calculations and checked the results with the electronic transition energies. The method of Pariser, Parr, and Pople[18,19] was used with an idealized model of the geometry (bond lengths and angles were taken from thiophene[20]). Standard parameters were used: for carbon, I_C = 11.22 eV, γ_{CC} = 10.53 eV, and β_{CC} = −2.318 eV; and for sulfur I_S = 20.0 eV, γ_{SS} = 10.84 eV, and β_{CS} = −1.623 eV.[21] Limited configuration interaction was included by taking 16 configurations resulting from excitation of one electron from each of the four highest occupied MO's to the four lowest vacant orbitals. The two-center integrals were evaluated according to Nishimoto and Mataga.[22] The observed and calculated electronic transitions are compiled in Table I.

The remarkable difference between the longest wavelength band of compound **2** (250 mμ) and the other compounds (around 300 mμ) is in accordance with the theoretical values. Compared with the bicyclic analogs, the thiophthenes,[23] no red shift is observed going from the bicyclic to the tricyclic systems. It also is remarkable that very little similarity exists between the spectra of the dithienothiophenes and the corresponding benzodithiophenes.[24,25]

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TABLE I
CALCULATED AND OBSERVED ELECTRONIC TRANSITIONS

Compd	λ_{max}, mμ Obsd (log ε)	Calcd (f)
1	282 (4.28),[a] 290 (4.40), 298 (4.24)[a]	212 (0.08), 218 (0.003), 232 (0.02), 242 (0.02), 290 (0.40), 301 (0.90)
2	215 (4.52), 233 (4.16), 250 (4.21)	207 (0.57), 219 (0.29), 238 (0.54), 247 (0.56), 259 (0.28), 272 (0.0003)
3	255 (4.22), 278 (4.14), 290 (4.21), 310 (3.00)	207 (0.08), 214 (0.23), 231 (0.005), 248 (0.37), 267 (0.67), 281 (0.30), 310 (0.03)
4	223 (4.42), 271 (4.05), 298 (3.70)	218 (0.54), 226 (0.78), 238 (0.01), 261 (0.10), 267 (0.33), 305 (0.33)

[a] Inflection.

Experimental Section

All experiments in which lithio compounds are used were conducted in a dry N_2 atmosphere. Melting points are uncorrected. Nmr spectra were obtained using a Varian A-60 spectrometer with TMS (τ 10) as an internal standard. Uv spectra were determined with a Zeiss PMQ II and infrared spectra with an Unicam SP 200. The microanalyses were carried out in the analytical section of this department under direction of Mr. W. M. Hazenberg.

Bis(phenylsulfonyl) Sulfide (6).[10]—To a stirred suspension of 25 g (0.155 mol) of sodium sulfinate in 400 ml of dry benzene was added a solution of 7.8 g (0.075 mol) of sulfur dichloride in 25 ml of benzene. The mixture was stirred at room temperature for 2 hr, and after filtration and evaporation of the solvent left a crystalline residue, which on recrystallization from benzene yielded 19 g (80%) of **6**, mp 128–130° (lit.[10] mp 133°).

3,3′-Dithienyl Sulfide (7).—A solution of 3-thienyllithium was prepared at −70° from 16.3 g (0.1 mol) of 3-bromothiophene[26] in 100 ml of absolute ether and 65 ml of 1.52 *N* ethereal *n*-BuLi (0.098 mol). In small portions 15.6 g (0.049 mol) of **6** was added. After stirring at −70° during 2 hr, the reaction mixture was allowed to warm and at 0° 10 ml of water was added. The lithium sulfinate was filtered and washed with ether, the combined ether layers were extracted with water, dried ($MgSO_4$), and concentrated, and the residue was distilled yielding 6.70 g (68%) of the sulfide **7**, bp 98–100° (0.08 mm), $n^{20}D$ 1.6720 [lit.[6] bp 115° (0.4 mm), $n^{25}D$ 1.6671].

Dithieno[3,2-*b*:2′,3′-*d*]thiophene (1).—To a stirred solution of 17.2 g (0.088 mol) of 3,3′-dithienyl sulfide (**7**) in 150 ml of absolute ether, 100 ml of a 1.72 *N* ethereal *n*-BuLi was added and heated under reflux for 1 hr. The mixture was cooled to 0°, transferred to a dropping funnel, and slowly added to a stirred, ice-cold suspension of 26 g (0.19 mol) of anhydrous $CuCl_2$ in 100 ml of absolute ether. The mixture was stirred at room temperature overnight, 100 ml of water was added, and the ether layer separated after filtration. After drying ($MgSO_4$) and concentration to a small volume, this reddish residue was purified over an alumina column using ether–pentane 1:1 as the eluent. Evaporation of the solvent left a solid residue, which on recrystallization from methanol yielded 8.9 g (52%) of **1**: mp 66–67° (lit.[4] mp 66.5–67.5°); nmr (CD_3COCD_3) δ 7.57 (d, 2, *J* = 5.0 Hz), 7.40 (d, 2, *J* = 5.0 Hz).

3,3′-Dibromo-2,2′-dithienyl Sulfide (9).—Starting from 54.0 g (0.22 mol) of 2,3-dibromothiophene[27] and 34.0 g (0.107 mol) of **6**, the procedure described for the synthesis of **7** yielded 30 g of a crude oil, which on distillation and recrystallisation from ether–pentane 1:1 furnished 22–26 g (61–70%) of **9**: bp 170–173° (0.08 mm); mp 54–55; uv max (EtOH) 256 mμ (log ε 4.16); nmr (CD_3COCD_3) δ 7.63 (d, 2, *J* = 5.2 Hz), 7.10 (d, 2, *J* = 5.2 Hz).

Anal. Calcd for $C_8H_4S_3Br_2$: C, 26.98; H, 1.13; S, 27.01; Br, 44.88. Found: C, 27.01; H, 1.10; S, 26.75; Br, 45.08.

Dithieno[2,3-*b*:3′,2′-*d*]thiophene (2).—A solution of 3,3′-dilithio-2,2′-dithienyl sulfide was prepared at −70° from 12.5 g (0.035 mol) of **9** in 100 ml of absolute ether and 50 ml of a 1.4 *N* ethereal *n*-BuLi solution (0.070 mol). After stirring at −70° for 45 min, the mixture was transferred to an externally cooled (−70°) dropping funnel and slowly added to a vigorously stirred suspension of 13 g (0.08 mol) of anhydrous $CuCl_2$ in 200 ml of absolute ether cooled to −50°. The mixture was stirred at −50° for 1 hr and then at room temperature overnight. After addition of 100 ml of water, the gray Cu_2Cl_2 precipitate was filtered, and the ether layer separated, washed with 2 *N* HCl and water, and dried over $MgSO_4$. After the ethereal solution was concentrated to a small volume, an alumina column was used for purification (eluent petroleum ether, bp 40–60°). The white solid obtained afforded on recrystallization from methanol 2.2 g (32%) of **2**: mp 84–86° (lit.[5] mp 85–86°); nmr (CD_3COCD_3) δ 7.58 (d, 2, *J* = 5.3 Hz), 7.48 (d, 2, *J* = 5.3 Hz).

4,4′-Dibromo-3,3′-dithienyl Sulfide (11). A. From 4-Bromo-3-thienyllithium (10) and 4,4′-Dibromo-3,3′-dithienyl Disulfide (12).—A solution of **10** in absolute ether was prepared at −70° from 41.2 g (0.17 mol) of 3,4-dibromothiophene[28] and 100 ml of a 1.5 *N* etheral *n*-BuLi solution. The mixture was transferred to an externally cooled (−70°) dropping funnel and added during 15 min to a stirred suspension of 58.0 g (0.15 mol) of **12** in 200 ml of absolute ether cooled to −70°. After stirring at −70° for 2 hr the disulfide **12** had disappeared and the mixture was allowed to warm up. At 0° 100 ml of water was added, and the ether layer was separated, extracted with 1 *N* NaOH, washed with water, and dried ($MgSO_4$). Evaporation of the ether and distillation yielded 44.3 g (83%) of **11** as a colorless oil: bp 164–165° (0.06 mm); $n^{25}D$ 1.7100; uv max (EtOH) 260 mμ (log ε 3.78); nmr (CD_3COCD_3) δ 7.33 (d, 2, *J* = 3.4 Hz), 7.62 (d, 2, *J* = 3.4 Hz).

Anal. Calcd for $C_8H_4S_3Br_2$: C, 26.98; H, 1.13; S, 27.01; Br, 44.88. Found: C, 26.81; H, 1.05; S, 27.20; Br, 44.94.

The aqueous layers were oxidized using the method described for the preparation of **12**, by which 25 g (86%) of the disulfide **12** could be reobtained, mp 65–68°.

B. From 4-Bromo-3-thienyllithium (10) and 6.—Starting from 24.2 g (0.1 mol) of 3,4-dibromothiophene[28] and 15.9 g (0.05 mol) of **6**, the procedure described for the synthesis of **7** yielded 11.2 g (63%) of the sulfide **11**.

Dithieno[3,4-*b*:3′,4′-*d*]thiophene (3).—From 26 g (0.074 mol) of **11**, 100 ml of a 1.5 *N* ethereal *n*-BuLi solution, and 26 g (0.16 mol) of anhydrous $CuCl_2$, the procedure described for the synthesis of **2** afforded 14 g of crude material, which on distillation yielded a solid. On recrystallization from *n*-hexane–ether 3:1, 4.5 g (31%) of **3** was obtained as long white needles: bp 118–120° (0.1 mm); mp 87–87.5°; nmr (CD_3COCD_3) δ 7.00 (d, 2, *J* = 2.6 Hz), 7.43 (d, 2, *J* = 2.6 Hz).

Anal. Calcd for $C_8H_4S_3$: C, 48.95; H, 2.06; S, 48.99. Found: C, 49.04; H, 2.13; S, 48.54.

4,4′-Dibromo-3,3′-dithienyl Disulfide (12).—The preparation of 4-bromo-3-thienyl thiolate parallels the synthesis of the corresponding thiol.[12] A solution of 4-bromo-3-thienyllithium (**10**) was prepared from 260 g (1.075 mol) of 3,4-dibromothiophene[28] and 600 ml of a 1.72 *N* etheral *n*-BuLi solution at −70°. In the course of 5 min 33 g (1.03 mol) of dry sulfur was added and after stirring at −70° for 1.5 hr the mixture was allowed to warm up. At −30° 100 ml of water was added and the ether layer extracted twice with a 100-ml portion of 2 *N* NaOH. The combined aqueous layers were washed with ether and then slowly added to a stirred, ice-cold solution of 600 g of $K_3Fe(CN)_6$ in 2.5 l. of water. The precipitate was filtered, washed with water, dissolved in dichloromethane, and dried ($MgSO_4$). Evaporation of the solvent yielded 168 g of **12** (mp 64–67°), which on further recrystallization from ether–CH_2Cl_2 1:1 gave 155 g (78%) of **12** as colorless prisms: mp 68–69°; uv max (EtOH) 225 mμ (log ε 4.14), 258 (3.91); nmr (CD_3COCD_3) δ 7.63 (d, 2, *J* = 3.5 Hz), 7.70 (d, 2, *J* = 3.5 Hz).

Anal. Calcd for $C_8H_4S_4Br_2$: C, 24.74; H, 1.03; S, 33.05; Br, 41.18. Found: C, 24.88; H, 0.97; S, 33.10; Br, 41.22.

3,4′-Dibromo-2,3′-dithienyl Sulfide (13).—From the reaction of 3-bromo-2-thienyllithium (**8**) [prepared at −70° from 18 g (0.074 mol) of 2,3-dibromothiophene[31] and 50 ml of a 1.5 *N* etheral *n*-BuLi solution] and 28.5 g (0.074 mol) of the disulfide **12**, 25 g (94%) of **13** were obtained: bp 168–172° (0.15 mm); uv max (EtOH) 254 mμ (log ε 4.07); nmr (CD_3COCD_3) δ 7.35 (d, 2, *J* = 3.4 Hz), 7.70 (d, 2, *J* = 3.4 Hz), 7.15 (d, 2, *J* = 5.6 Hz), 7.63 (d, 2, *J* = 5.6 Hz).

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(28) S. Gronowitz, P. Moses, and R. Hakansson, *ibid.*, **16**, 267 (1960).

Anal. Calcd for $C_8H_4S_3Br_2$: C, 26.98; H, 1.13; S, 27.01; Br, 44.88. Found: C, 27.24; H, 1.22; S, 27.35; Br, 44.72.

On oxidation of the aqueous layers with 40 g of $K_3Fe(CN)_6$ as described for the synthesis of **12**, 12.2 g (85%) of the disulfide **12** could be reobtained, mp 66–68°.

Dithieno[2,3-*b*:3′,4′-*d*]thiophene (4).—Starting from 13.4 g (0.038 mol) of **13** and 50 ml of a 1.5 *N* ethereal *n*-BuLi solution, the dilithio derivative was prepared at −70°. The usual oxidative ring closure with 13 g (0.08 mol) of anhydrous $CuCl_2$ yielded a yellow oil, which on distillation furnished a solid, which was recrystallised from ether–pentane 1:3, giving 2.1 g (29%) of **4** as colorless needles: bp 114–116° (0.07 mm); mp 76–77°; nmr (CD_3COCD_3) δ 7.17 (d, 2, J = 5.5 Hz), 7.33 (d, 2, J = 5.5 Hz), 7.25 (d, 2, J = 2.6 Hz), 7.31 (d, 2, J = 2.6 Hz).

Anal. Calcd for $C_8H_4S_3$: C, 48.95; H, 2.06; S, 48.99. Found: C, 48.67; H, 2.14; S, 48.92.

Dithieno[3,2-*b*:2′,3′-*d*]thiophene 4,4-Dioxide[4] (15).—From 196 mg (1 mmol) of **1** dissolved in 15 ml of acetic acid and 3 ml of 30% H_2O_2, 130 mg (57%) of **15** was obtained after stirring for 30 hr at room temperature: mp 248–249° (lit.[4] mp 251.5–253°); uv max (EtOH) 236 mμ (log ε 4.06), 243 (4.06), 354 (3.78); nmr (CD_3COCD_3) δ 7.37 (d, 2, J = 5.0 Hz), 7.73 (d, 2, J = 5.0 Hz); ir (KBr) 1130, 1285 cm^{-1} (SO_2).

Dithieno[3,4-*b*:3′,4′-*d*]thiophene 4,4-Dioxide (16).—In 50 ml of dry dichloromethane 588 mg (3 mmol) of **3** and 1.20 g (7 mmol) of *m*-chloroperbenzoic acid were dissolved. The mixture was allowed to stand 14 hr at −10°, the solvent was evaporated, and the solid residue was washed with 10 ml of a saturated $NaHCO_3$ solution. After the residue was recrystallized from dioxane–water 1:1, 500 mg (70%) of **16** was obtained as long white needles: mp 239–240°; uv max (EtOH) 226 mμ (log ε 4.40), 234 (4.41), 243 (4.39), 271 (3.86), 294 (3.69); nmr (CD_3COCD_3) δ 7.77 (d, 2, J = 2.4 Hz), 8.13 (d, 2, J = 2.4 Hz); ir (KBr) 1130, 1290 cm^{-1} (SO_2).

Anal. Calcd for $C_8H_4S_3O_2$: C, 42.08; H, 1.76; S, 42.13. Found: C, 42.03; H, 1.84; S, 42.35.

Dithieno[2,3-*b*:3′,2′-*d*]thiophene 7,7-Dioxide (17).—From 588 mg (3 mmol) of **2** and 1.20 g (7 mmol) of *m*-chloroperbenzoic acid the procedure described for the preparation of **16** afforded 342 mg (50%) of the sulfone **17** as white needles from methanol: mp 193–195°; uv max (EtOH) 223 mμ (log ε 4.31), 285 (3.91), 335 (2.99); nmr (CD_3COCD_3) δ 7.38 (d, 2, J = 5.0 Hz), 8.00 (d, 2, J = 5.0 Hz); ir (KBr) 1150, 1305 cm^{-1} (SO_2).

Anal. Calcd for $C_8H_4S_3O_2$: C, 42.08; H, 1.76; S, 42.13. Found: C, 42.68; H, 2.00; S, 42.54.

Dithieno[2,3-*b*:3′,4′-*d*]thiophene 7,7-Dioxide (18).—By the method described for the preparation of **16**, from 500 mg (2.55 mmol) of **4** and 1.1 g (6.4 mmol) of *m*-chloroperbenzoic acid 370 mg (64%) of **18** was obtained as white needles from dioxane–water 1:1: mp 210–211°; uv max (EtOH) 236 mμ (log ε 4.24), 256 (4.00), 264 (4.16), 304 (3.08); nmr (CD_3COCD_3) δ 8.15 (d, 2, J = 2.4 Hz), 7.68 (d, 2, J = 2.4 Hz), 7.80 (d, 2, J = 5.0 Hz), 7.62 (d, 2, J = 5.0 Hz); ir (KBr) 1140, 1290 cm^{-1} (SO_2).

Anal. Calcd for $C_8H_4S_3O_2$: C, 42.08; H, 1.76; S, 42.13. Found: C, 42.07; H, 1.84; S, 42.08.

Dithieno[3,4-*b*:3′,4′-*d*]thiophene 4-Oxide (19).—To a solution of 196 mg (1 mmol) of **3** in 20 ml of acetic acid was added 2 ml of a 30% H_2O_2 solution. After the solution was stirred at room temperature for 5.5 hr, 40 ml of water was added, and the crystalline material was filtered and recrystallized from methanol yielding 160 mg (75%) of **19** as white needles: mp 203–204°; uv max (EtOH) 220 mμ (log ε 4.41), 242 (4.40), 248 (4.41), 268 (3.88), 278 (3.84), 298 (3.47); nmr (CD_3COCD_3) δ 7.71 (d, 2, J = 2.4 Hz), 8.18 (d, 2, J = 2.4 Hz); ir (KBr) 1030 cm^{-1} (S=O).

Anal. Calcd for $C_8H_4S_3O$: C, 45.26; H, 1.89; S, 45.31. Found: C, 45.08; H, 2.02; S, 44.87.

Registry No.—**1**, 3593-75-7; **2**, 236-63-5; **3**, 13090-49-8; **4**, 28504-79-2; **9**, 28504-80-5; **11**, 28504-81-6; **12**, 28504-82-7; **13**, 28504-83-8; **15**, 3807-53-2; **16**, 28504-85-0; **17**, 28504-86-1; **18**, 28504-87-2; **19**, 28504-88-3.

Solvolyses of 2α,5-Epithio-5α- and -Epoxy-5α-cholestane Derivatives. A Reactivity Factor of 10^{11} Due to Sulfur Participation in a 7-Thiabicyclo[2.2.1]heptane Derivative

TERUJI TSUJI, TAICHIRO KOMENO, HIKARU ITANI, AND HIROSHI TANIDA*

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

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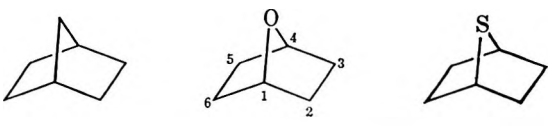
Solvolysis reactions of 2α,5-epithio-5α-cholestanes, a corresponding sulfoxide, and 2α,5-epoxy-5α-cholestanes bearing a bromo or methanesulfonyloxy group at the C-3 exo (α) or endo (β) reaction site were investigated in aqueous dioxane and compared with the solvolyses of *exo*- and *endo*-2-norbornyl methanesulfonates (**12** and **13**). Rates of exo derivatives of the epithiocholestane (**6**), the epoxycholestane (**9**), and 7-oxabicyclo[2.2.1]heptane (**1**) are of the same order of magnitude and about 10^3 times less than that of **12**. The products were those expected to result from Wagner–Meerwein rearrangement of the C(1)–C(2) bond, the hemithioacetal **14** (formed by cyclization of a *cis*-mercaptoaldehyde) from **6** and the *cis*-hydroxyaldehyde **16** from **9**. The small reactivities of **6** and **9** relative to **12** are considered to arise from the inductive effect of the oxygen or the sulfur bridge and the effects of bridging C-5 with C-10 (exo) by the B ring are indicated to be unimportant. The *endo*-epithiocholestane (**5**) solvolyzes with a very fast rate which is, in 70% dioxane, 1.1×10^{10} times the rate of *endo*-epoxycholestane (**8**) and 1.2×10^8 times that of **6**. A product of retention of configuration is exclusively formed from **5**. The results are interpreted in terms of participation of the sulfur atom, greatly enhanced by its geometric situation in the steroidal [2.2.1] system. Conversion of **5** to its sulfoxide **7** results in a disappearance of the sulfur participation. Whereas the *endo*-7-oxabicyclo[2.2.1]heptane (**2**) undergoes a Wagner–Meerwein rearrangement, **8** produces mainly a product of retention of configuration. This retention is discussed as being indicative of a small degree of participation of oxygen.

The ring system most extensively studied in connection with the interest in the role of neighboring group participation in carbonium ion reactions is the bicyclo[2.2.1]heptane system.[1] Effects of the replacement of the 1,4-methylene bridge in this system by

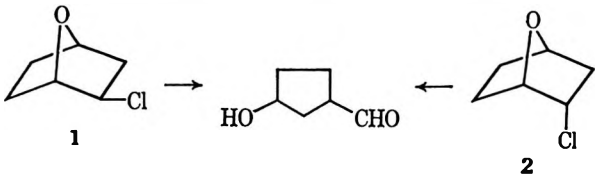


an oxygen bridge were first investigated by Martin and Bartlett[2] by the solvolyses of 7-oxabicyclo[2.2.1]-hept-2(*exo* and *endo*)-yl chlorides (and bromides).

(1) (a) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N. Y., 1965; (b) J. A. Berson, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N Y., 1963, Chapter 3; (c) C. D. Sargent, *Quart. Rev. (London)*, **20**, 301 (1966).

(2) J. C. Martin and P. D. Bartlett, *J. Amer. Chem. Soc.*, **79**, 2533 (1957).

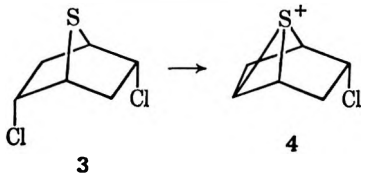
They found that the exo chloride **1** is less reactive than *exo*-2-norbornyl chloride by a factor of approxi-



1 **2**

mately 2000 and that the endo chloride **2** solvolyzes 160 times more slowly at 140° than **1**. In either case, the solvolysis product was that expected to result from rearrangement, 3-formylcyclopentanol. These workers' interpretation of the results was that the replacement of the methano bridge by the oxygen bridge causes the adverse inductive effect by the oxygen atom, with no capability for participation by the oxygen atom, and that the anchimeric assistance of ionization, as proposed for *exo*-2-norbornyl chloride, is not greatly affected by the replacement.

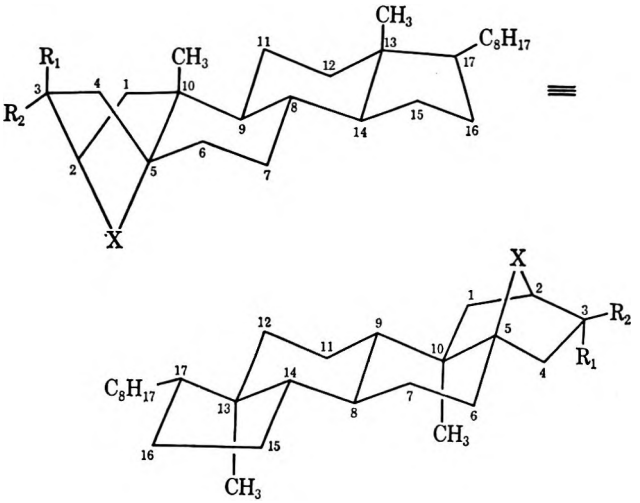
A neighboring sulfur atom has long been known as a very effective participating group[3] and, in appropriate cases, participation by sulfur has been found to be much greater than that by oxygen.[4] However, recent evidence in some bridged polycyclic systems demonstrates that the ability of sulfur to participate is greatly influenced by the stereochemistry of the leaving group and the internuclear distance from the developing electron-deficient center.[5,6] For these reasons, we have been interested in the solvolysis of 7-thiabicyclo[2.2.1]heptane derivatives, in which the methylene bridge in bicyclo[2.2.1]heptane is replaced by the sulfur bridge. Corey and Block[7] succeeded in a convenient synthesis of 7-thiabicyclo[2.2.1]heptanes and found that one of these compounds, 2,5-bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane (**3**), solvolyzed with a very fast rate and gave a stereospecific product. Although they suggested that these results were indicative of intervention of a sulfonium ion intermediate (**4**), since their research was directed toward



3 **4**

the development of synthetic methods, they reported neither the kinetic data on **3** nor the solvolytic behavior of the exo counterpart.

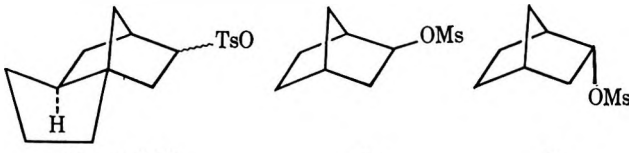
Recently, 2α,5-epithio-5α-cholestanes (**5** and **6**) and the related sulfoxide (**7**), and 2α,5-epoxy-5α-cholestanes (**8**, **9**, and **10**) bearing groups suitable for solvolysis, bromo or methanesulfonyloxy, at C-3, became available in our laboratory.[8] These steroidal compounds have the 7-thia- or 7-oxabicyclo[2.2.1]heptane system in the A ring and the substituents at C-3 make sets of exo (α) and endo (β) epimers. Corrections due only to the difference between the leaving bromo and methanesulfonyloxy groups will be needed for discussion of the relative reactivities. Furthermore, the



5, X = S; R_1 = Br; R_2 = H
6, X = S; R_1 = H; R_2 = OSO_2CH_3
7, X = SO; R_1 = Br; R_2 = H
8, X = O; R_1 = OSO_2CH_3; R_2 = H
9, X = O; R_1 = H; R_2 = OSO_2CH_3
10, X = O; R_1 = H; R_2 = Br

(R_1, β or endo; R_2, α or exo)

bridgehead C-5 and the C-10 exo (or α) positions in the [2.2.1] moiety are linked by the four-carbon chain of the B ring. Interest in such a linkage in the [2.2.1] system was exemplified by Corey and Glass[9] by the solvolysis of *exo*- and *endo*-4,5-*exo*-trimethylene-2-norbornyl tosylates (**11**), in which a trimethylene chain connects the corresponding C-4 bridgehead and the C-5 exo positions. Therefore, to investigate the effect of the B ring on the solvolysis of the steroids would be also of considerable interest. These considerations led us to initiate the present work.



11e, *exo*-TsO **12** **13**
11n, *endo*-TsO

Results

Solvolysis Rates.—Rates of hydrolysis of the steroids **5**–**10** and, as reference compounds, *exo*- and *endo*-norbornyl methanesulfonates (mesylates) (**12** and **13**) were measured in aqueous dioxane containing varying amounts of water and 1.1 equiv of sodium acetate, by titrating at intervals the methanesulfonic acid or the hydrobromic acid liberated during the reaction. The observed kinetics were first order in all cases, and the experimental infinity titers at about ten half-lives corresponded to the calculated values. Since we failed to prepare the epithio β-mesylate (X = S, R_1 = OSO_2CH_3, R_2 = H), the solvolyses of the less reactive bromides (**5** and **7**) were carried out. Rate constants

(3) (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, 1962, pp 108–110; (b) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964).

(4) For example, M. Hojo, T. Ichi, Y. Tamaru, and Z. Yoshida, *J. Amer. Chem. Soc.*, **91**, 5170 (1969).

(5) R. E. Ireland and H. A. Smith, *Chem. Ind. (London)*, 1252 (1959).

(6) L. A. Paquette, G. V. Meehan, and L. D. Wise, *J. Amer. Chem. Soc.*, **91**, 3231 (1969).

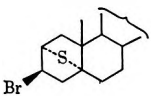
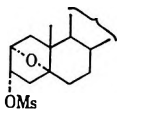
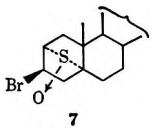
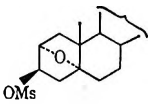
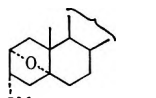
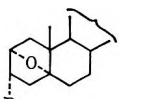
(7) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).

(8) (a) T. Komeno and H. Itani, *Chem. Pharm. Bull.*, **18**, 608 (1970); (b) T. Komeno, H. Itani, H. Iwakura, and K. Nabeyama, *ibid.*, **18**, 1145 (1970); (c) Y. Komeno, M. Kishi, and K. Nabeyama, *Tetrahedron*, in press; T. Komeno and M. Kishi, to be published.

(9) E. J. Corey and R. S. Glass, *J. Amer. Chem. Soc.*, **89**, 2600 (1967).

TABLE I

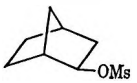
SOLVOLYSIS OF 2α,5-EPITHIO-5α- AND -EPOXY-5α-CHOLESTANE DERIVATIVES IN AQUEOUS DIOXANE

Compd[a]	Vol % of dioxane[b]	Temp, °C	k, sec^{-1}	Calcd at 25°: $\Delta H^{\pm}$, kcal	Calcd at 25°: $\Delta S^{\pm}$, cal/deg	Calcd at 25°: k, sec^{-1}
 5	90	5.0	2.39×10^{-5}	17.30	−17.4	2.04×10^{-4} [c]
	90	15.0	6.82×10^{-5}			
	90	25.0	2.09×10^{-4}			
	80	5.0	5.34×10^{-4}			
	70					4.12×10^{-2} [d]
 6	90	119.5	2.35×10^{-5}	27.50	−10.2	2.60×10^{-10}
	90	151.2	3.46×10^{-4}			
	70	90.7	3.17×10^{-5}	25.70	−8.9	1.05×10^{-8}
	70	119.5	4.56×10^{-4}			
	60					3.82×10^{-8} [d]
 7	60	130.2	2.02×10^{-5}	21.92	−26.2	1.00×10^{-9}
	60	160.3	1.42×10^{-4}			
 8	70	119.8	2.99×10^{-5}	30.07	−3.2	1.14×10^{-10}
	70	149.9	4.89×10^{-4}			
 9	90	119.3	7.78×10^{-5}	25.93	−11.8	1.66×10^{-9}
	90	149.0	8.52×10^{-4}			
	70	80.2	4.35×10^{-6}	22.64	−14.7	9.50×10^{-8}
	70	109.7	5.56×10^{-4}			
	80					1.78×10^{-8} [d]
 10	80	157.2	4.24×10^{-4}	25.39	−15.6	5.98×10^{-10}
	80	127.7	4.53×10^{-5}			

[a] [R—X] = 4.0×10^{-3} M. [b] Containing 1.1 equiv of CH_3COONa. [c] Calculated from the observed rates using the least-squares method. [d] Extrapolated by the Grunwald-Winstein equation, $\log k/k_0 = mY$. We obtained the following m values: for **5**, 1.13 at 5°; for **6**, 0.79 at 25°; for **9**, 0.86 at 25°.

TABLE II

SOLVOLYSIS OF 2-NORBORNYL METHANESULFONATE IN AQUEOUS DIOXANE

Compd[a]	Vol % of dioxane[b]	Temp, °C	k, sec^{-1}	Calcd at 25°: $\Delta H^{\pm}$, kcal	Calcd at 25°: $\Delta S^{\pm}$, cal/deg	Calcd at 25°: k, sec^{-1}	*exo/endo* rate ratio
 12	90	80.1	5.07×10^{-4}	21.15	−14.2	1.68×10^{-6}	180 (90% dioxane)
	90	50.2	2.91×10^{-5}				
	70	25.0	1.21×10^{-4}			1.21×10^{-4}	880 (70% dioxane)
 13	90	129.9	3.69×10^{-4}	23.53	−16.5	9.42×10^{-9}	
	90	100.0	3.32×10^{-5}				
	70	100.0	7.08×10^{-4}	24.64	−7.5	1.38×10^{-7}	
	70	69.9	3.60×10^{-5}				

[a] [R—X] = 8.0×10^{-3} M. [b] Containing 1.1 equiv of CH_3COONa.

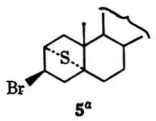
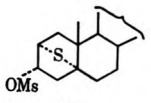
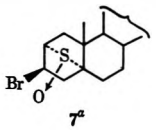
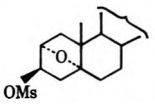
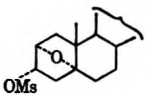
thus obtained for the steroids are summarized in Table I and those of **12** and **13** in Table II. For comparison of the relative reactivities, the rate constants were extrapolated to 25° by the Arrhenius equation, the rate of **5** in 70% aqueous dioxane and that of **6** in 60% aqueous dioxane were calculated by the Grunwald-Winstein equation, $\log k/k_0 = mY$,[10] and the rate factor, $k_{OSO_2CH_3}/k_{Br} = 30$, obtained from the hydrolyses of **9** and **10** in 80% aqueous dioxane, was used for correction of the leaving group effects. Table III lists the relative reactivities choosing that of **6** as unity.

For product determination, the hydrolyses were carried out for ten half-lives under the same conditions as used for the rate studies. Hydrolysis of **5** in 90% dioxane at a room temperature was found to give the product of retention of configuration, the endo alcohol and its acetate, without any other detectable compound. Hydrolysis of **6** in 70% dioxane caused rearrangement forming mainly a hemithioacetal, for which the structure **14** was assigned. The nmr spectrum shows a doublet at τ 5.25 (J = 1.6 Hz), assignable to a proton attached to the carbon bearing the

(10) J. F. Bunnett, "Technique of Organic Chemistry," Vol. 8, part 1, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, Chapter 6, pp 240–245.

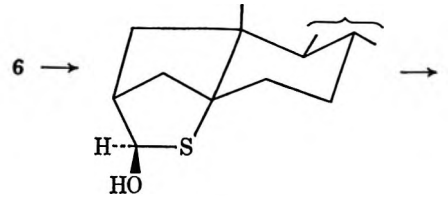
Table III

Relative Reactivity at 25°

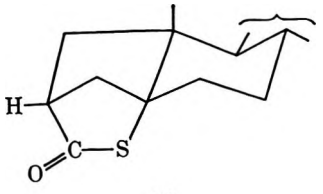
Vol % of dioxane	 5[a]	 6	 7[a]	 8	 9
90	2.3×10^7	1.0			6.4
70	1.2×10^8	1.0		0.011	9.0
60		1.0	0.79		

[a] The rate for the corresponding methanesulfonate was estimated by use of the factor, methanesulfonate; bromide = 30, obtained from the solvolysis of the epoxy α derivatives (9 and 10).

hydroxyl group, and a broad doublet at τ 7.44 (J = 6.0 Hz), assignable to the bridgehead proton. Vicinal coupling constants in the bicyclo[2.2.1]heptane system have been well investigated.[11] The constants between the C-1 bridgehead proton and the C-2 (endo) proton in this system are usually found in the range 0–2 Hz, while those between the bridgehead proton and the C-2 (exo) proton in the range 3–6 Hz. On the basis of these data, the hydroxyl group in **14** was determined as the exo orientation. Oppenauer oxidation of **14** gave a bridged γ-thiolactone **15**, whose CD curve exhibits a negative sign of the n–π* Cotton effect at 280 mμ.[12]



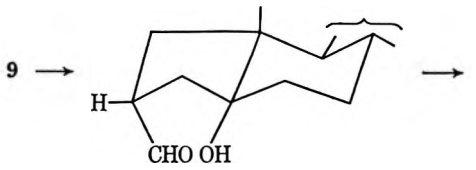
14



15

The products from the sulfoxide **7** were not investigated in detail because of their apparent complexity.

Hydrolysis of **8** in 70% dioxane led to three products, separable by preparative layer chromatography, whose yields were determined as 86.8, 1.8, and 0.9%, respectively. The structures for the 86.8% and 0.9% products were determined to be, respectively, the alcohol of retention (R_1 = OH in **8**) and the alcohol of inversion (R_2 = OH in **9**). The structure of the product of 1.8% yield was found to be identical with the predominant product from **9**, mentioned next. Hydrolysis of **9** in 70% dioxane fromed a rearranged product in 80% yield, whose structure was assigned as the *cis*-hydroxyaldehyde (**16**) by spectral data. The nmr spectrum shows a doublet due to the secondary aldehyde proton at τ 0.26 (J = 2.0 Hz). The orientation of the aldehyde group was demonstrated by the fact that oxidation of **16** with Jones reagent in acetone gave a bridged γ lactone (**17**), showing an infrared carbonyl band at 1784 cm^{-1} and a negative n–π* Cotton effect curve ([θ] −1490 at 219 mμ), as predicted from the lactone sector rule.[13]



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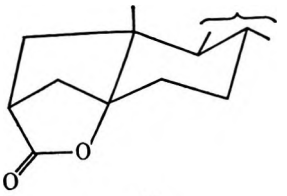

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Discussion

First, the reactivities of the exo compounds are discussed. In Table I the rates of the epithio exo (**6**) and the epoxy exo (**9**) compounds are found to be of the same order of magnitude, so that replacement of the oxygen bridge by the sulfur bridge in these steroidal C-3 exo systems is unimportant in solvolysis. The chloride **1** was reported to be 2000 times less reactive than *exo*-2-norbornyl chloride and comparison of the data in Tables I and II indicates that **9** is less reactive than **12** in 70% dioxane by approximately the same factor, 1300. In addition, nearly identical reactivities were predicted for 7-oxabicyclo[2.2.1]hept-2(*exo*)-yl bromide and **10** by a rough calculation based on available rate constants: for the former bromide, $k_1 = 7.4 \times 10^{-9}$ sec^{-1} at 25° in 50% dioxane[2] (the reported data were extrapolated to 25°); for **10**, $k_1 = 5.98 \times 10^{-10}$ sec^{-1} at 25° in 80% dioxane.[14] It is, therefore, suggested that a factor(s) responsible for the diminished reactivity of the **1** derivatives relative to the *exo*-2-norbornyl derivatives is also effective for **9** and **10** and that the B ring connecting the C-5

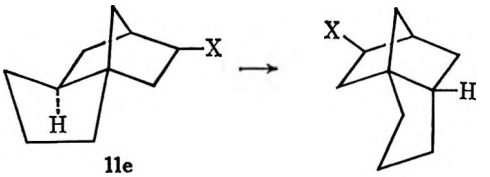
(11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 288–289; J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); J. E. Franz, C. Osuch, and M. W. Dietrich, *J. Org. Chem.*, **29**, 2922 (1964).

(12) (a) K. Kuriyama, K. Komeno, and K. Takeda, *Shionogi Kenkyusho Nempo*, **17**, 66 (1967); (b) K. Takeda, K. Kuriyama, T. Komeno, D. A. Lightner, R. Records, and C. Djerassi, *Tetrahedron*, **21**, 1203 (1965).

(13) J. P. Jennings, W. Klyne, and P. M. Scopes, *Proc. Chem. Soc., London*, 412 (1964); *J. Chem. Soc.*, 7211 (1965).

(14) Since, for 7-oxabicyclo[2.2.1]hept-2(*exo*)-yl bromide, the rate constants at 85° of 8.58×10^{-7} sec^{-1} in 80% ethanol and 8.24×10^{-6} sec^{-1} in 50% dioxane have been reported,[2] an application of the Grunwald–Winstein equation gives m = 0.725. Assuming that m is independent of reaction temperature, this m value and the rate in 50% dioxane give a rate constant of 1.95×10^{-10} sec^{-1} at 25° in 80% dioxane. Therefore, the relative reactivities for 7-oxabicyclo[2.2.1]hept-2(*exo*)-yl bromide and **10** are 1 to 3.

bridgehead with the C-10 exo position is not a significant factor in the present steroidal oxa system. For the diminished reactivity of the oxa compounds, the inductive effect of the oxygen atom seems to be the most important, as postulated by Martin and Bartlett.[2] The large rate decrease and the inhibition of Wagner–Meerwein rearrangement (**11e** → **18**) resulting from the trimethylene linkage in **11e**[9] is in sharp contrast

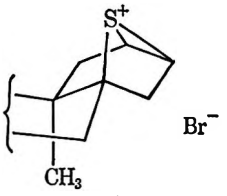


11e **18**

with the absence of such effects in the case of bridging due to the B ring. It has been proposed that, in the case of **11e**, the Wagner–Meerwein rearrangement accompanying the solvolysis steadily increases strain energy and also that such an increase of strain would be diminished to a small value when the number of bridge atoms is large (longer than a trimethylene chain).[9] Although it is not simple in such complex molecules as the present steroids to estimate the difference in strain between the starting compound and the product formed with Wagner–Meerwein rearrangement, inspection of Fieser–Dreiding molecular models suggests that the strain difference is not serious, in accord with our observations.

The formation of products in the exo solvolysis is mechanistically uniform; the occurrence of Wagner–Meerwein rearrangement was observed in all cases and, as a result, the hemithioacetal **14** and the *cis*-hydroxyaldehyde **16** were formed from **6** and **9**, respectively. These results are similar to that from **1**.

The epithio endo compound **5** is enormously more reactive than the exo counterpart **6** and the oxa analog **8**. After correction for the difference of leaving groups (Br *vs.* OSO_2CH_3), the endo/exo reactivity ratio is 2.3×10^7 in 90% dioxane and 1.2×10^8 in 70% dioxane and the reactivity ratio of **5** to **8** is 1.1×10^{10} in 70% dioxane (Table III). In the oxa-bridged series the exo isomer **9** hydrolyzes in 70% dioxane 820 times faster than the endo isomer **8**. It is noted that this exo/endo rate ratio is quite comparable to that found in the norbornyl system (880 in the same solvent). Since it can be considered that the rate for **6** involves an acceleration by C(1)–C(2) bond participation [equivalent to C(1)–C(6) bond participation in the norbornyl system], to a degree indicated by the exo/endo rate ratio, a real rate enhancement in **5** may amount to a huge factor of $\sim 10^{11}$ correcting the apparent factor of 1.2×10^8 in 70% dioxane for the exo/endo rate ratio. Furthermore, the high reactivity of **5** completely vanishes on transformation of **5** into the sulfoxide **7**. Therefore, it is apparent that the sulfur atom in **5** exerts a remarkable driving force during ionization of the C–Br bond. The solvolysis process of **5** can be formulated as involving direct interaction of the lone pair electrons on the sulfur with the developing cationic center at C-3 to stabilize the transition state and thereby would lead directly to such a three-membered sulfonium ion as **19**. Such participation of the



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sulfur agrees with the observed exclusive formation of the retained product in a stereospecific manner.

The steroidal epoxy endo **8** is less reactive than the *endo*-norbornyl **13** by a factor of 1200 in 70% dioxane. The exo/endo rate ratios are 820 in the steroidal epoxy system, 880 in the norbornyl system, and 160 in the 7-oxabicyclo[2.2.1]heptyl system [although in the last system the leaving group, the reaction solvent, and the temperature used (140°) were different]. All the ratios are of the same order of magnitude. However, whereas the products from the 7-oxa[2.2.1] **2** and the norbornyl **13** involve Wagner–Meerwein rearrangement, the hydrolysis of **8** resulted mainly in formation of the retained product. A possible explanation is that the retention of configuration from **8** is a result of participation of the oxygen. Although the major factor influencing the observed reactivities of **8** and the exo counterpart **9** is the great rate-retarding inductive effect of the oxygen, both these reactions are affected additionally by much smaller rate-accelerating factors, oxygen participation in the case of **8** and rearrangement to an alkoxycarbonium ion with **9**. The "normal" exo/endo rate ratios for the above 7-oxa compounds might result from cancellation of these two rate-accelerating factors. The geometric constraints in **8** imposed by its fused steroidal skeleton prevent rearrangement to the alkoxycarbonium ion and result in retention of configuration, while **2** is not geometrically restrained from rearrangement to a stable alkoxycarbonium ion. Nevertheless, if the oxygen exerts a significant product control after an unassisted ionization, the present results from **8** can be accommodated without the proposal of oxygen participation. A classical cation with a charge situated at the C-3 position could not be transformed into the alkoxycarbonium ion due to the geometric constraints.

Experimental Section

All melting points were taken on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer polarimeter, type 141, in chloroform containing 1% of ethanol. Ir spectra in Nujol mulls were measured by use of a Koken DS-201B spectrophotometer. CD and ORD curves were determined with a Jasco Model ORD/UV-5 equipped with CD. All nmr spectra were run in deuteriochloroform solutions with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. For preparative tlc, silica gel G (E. Merck Co.) was used as an adsorbent.

Materials.—Preparation and structural elucidation of the materials (**5**–**10**) used for hydrolysis were reported elsewhere.[8] The physical properties and elementary analyses are listed in Table IV.

***exo*-2-Norbornyl Mesylate** (**12**).—*exo*-2-Norbornanol[15] was dissolved in cold pyridine, treated with a slight excess of mesyl chloride, and allowed to stand in a refigerator overnight. After being poured into cold water, the reaction mixture was extracted with ether, washed successively with dilute sulfuric acid, sodium carbonate solution, and water, and dried over sodium

(15) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **81**, 4106 (1959).

Table IV

Compd	Mp, °C	[α]D, deg (°C)[a]	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S or Br, % Calcd	S or Br, % Found
5	88–89	+43.1 (24)	$C_{27}H_{45}BrS$	67.33	67.34	9.42	9.44	16.59[b]	16.62
6	120–121.5	−24.9 (21)	$C_{28}H_{48}O_3S_2$	67.69	67.46	9.74	9.67	12.91	12.81
7	94–95	+79.9 (22)	$C_{27}H_{45}OSBr$	65.17	65.08	9.12	9.14	16.06[b]	15.98
8	128–129.5	+28.7 (23)	$C_{28}H_{48}O_4S$	69.95	69.97	10.06	10.13	6.70	6.80
9	116–118	+13.2 (19)	$C_{28}H_{48}O_4S$	69.95	70.05	10.06	10.02	6.70	6.78
10	122–124	+23.6 (22)	$C_{27}H_{45}OBr$	69.66	69.66	9.74	9.69	17.17[b]	17.35

[a] Measured in chloroform solution containing 1% ethanol. [b] Calculated value for bromine.

sulfate. Evaporation of the ether under reduced pressure gave **12** as an oil, which was used for hydrolysis at once, $n^{25}D$ 1.4766.

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42; S, 16.86. Found: C, 50.56; H, 7.49; S, 16.50.

endo-2-Norbornyl Mesylate (13).—According to the same procedure, **13** was obtained as an oil from *endo*-2-norbornanol,[16] $n^{25}D$ 1.4802.

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.42; S, 16.86. Found: C, 50.22; H, 7.38; S, 17.08.

Hydrolysis of 3β-Bromo-5α-cholestane 2α,5-Episulfide (5).—A solution of 100 mg (0.21 mmol) of **5** in 53 ml of 90% aqueous dioxane containing 0.23 mmol of sodium acetate was allowed to stand overnight at room temperature. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with methylene dichloride, and the methylene dichloride solution was dried over sodium sulfate. After removal of the solvent, the residue, which exhibited two spots on tlc, was separated by preparative tlc with cyclohexane–ethyl acetate (3:1) to yield 40 mg (41.8%) of **5**-OAc, mp 120.5–121°, and 36 mg (41.4%) of **5**-OH, mp 149–150°, the properties of which were identical with the reported data.[8c]

Hydrolysis of 3α-Mesyloxy-5α-cholestane 2α,5-Episulfide (6).—A mixture of 900 mg (1.81 mmol) of **6** in 70 ml of dioxane and 364 mg (4.44 mmol) of sodium acetate in 30 ml of water was heated in a sealed tube at 90° for 61 hr. The work-up as used for **5** afforded 800 mg of crude products, which were chromatographed over 80 g of silica gel. The fractions eluted with benzene–ether (9:1) gave 396 mg of the hemithioacetal **14** as colorless crystals in a yield of 52.2%. Recrystallization from acetone afforded a pure sample, mp 145–146°, $[\alpha]^{23}D$ −52.3 ± 1.8° (*c* 0.524).

The infrared absorptions due to OH appeared at 3598, 3450, 1040, 1030, and 1015 cm^{-1}. The nmr spectrum showed τ 9.33 (s, 3 H of 13-CH_3), 9.04 (s, 3 H of 10-CH_3), 7.44 (d, J = 6.0 Hz, 1 H of 2β-H), and 5.25 (d, J = 1.6 Hz, 1 H of SCH).

Anal. Calcd for $C_{27}H_{46}OS$: C, 77.45; H, 11.07; S, 7.66. Found: C, 77.29; H, 11.10; S, 7.65.

5-Mercapto-*A*-nor-5α-cholestane-2α-carboxylic Acid Lactone (15).—A mixture of 150 mg (0.359 mmol) of **14**, 72 mg (0.353 mmol) of aluminum isopropoxide, and 1.2 ml (11.4 mmol) of cyclohexanone in 15 ml of dry benzene was heated under reflux for 1 hr. After addition of an aqueous solution of sodium potassium tartrate tetrahydrate, the reaction solution was extracted with methylene dichloride. The methylene dichloride extract was washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to preparative tlc, developing with cyclohexane–ethyl acetate (4:1). The less mobile fraction gave 30 mg (20%) of the starting material **14**. The more mobile fraction afforded 110 mg of γ-thiolactone **15** in a yield of 72.9%, which was recrystallized from acetone yielding a pure sample: mp 126–127°; $[\alpha]^{23}D$ +41.0 ± 1.5° (*c* 0.524); CD (isooctane) $[\theta]_{280}$ −4377, $[\theta]_{272}$ −4445, $[\theta]_{237}$ +36560, $[\theta]_{218}$ −14510, $[\theta]_{205}$ +6890; ORD (isooctane) $[\phi]_{400}$ +440, $[\phi]_{350}$ +684, $[\phi]_{300}$ +646, $[\phi]_{247}$ +28750, $[\phi]_{226}$ −37380, $[\phi]_{205}$ +11710. The infrared spectrum showed an absorption of CO at 1706 cm^{-1}. The nmr spectrum showed τ 9.31 (s, 3 H of 13-CH_3), 8.91 (s, 3 H of 10-CH_3), and 7.16 (m, 1 H of 2β-H).

Anal. Calcd for $C_{27}H_{44}OS$: C, 77.63; H, 10.62; S, 7.67. Found: C, 77.24; H, 10.58; S, 7.74.

Hydrolysis of 3β-Mesyloxy-5α-cholestane 2α,5-Epoxide (8).—To a solution of 1.0 g (2.08 mmol) of **8** in 70 ml of dioxane was added a solution of 264 mg (3.22 mmol) of sodium acetate in 30 ml of water, and the mixture was heated in a sealed tube at 120° for 64 hr. After the usual work-up, 864 mg of crystalline products obtained were chromatographed through 85 g of silica gel using a fraction collector. Elution with chloroform–ethyl acetate (9:1) gave four kinds of products roughly separated, which were further purified by preparative tlc to yield 15 mg (1.8%) of the hydroxyaldehyde **16**, 27 mg (2.5%) of the starting mesylate **8**, 7 mg (0.9%) of **9**-OH, and 727 mg (86.8%) of the retained alcohol **8**-OH.

Hydrolysis of 3α-Mesyloxy-5α-cholestane 2α,5-Epoxide (9).—Hydrolysis of 1.0 g (2.08 mmol) of **9** was carried out (80°, 45 hr) similarly as described for **8**, furnishing 840 mg of a crude material. This material was purified by chromatography over 84 g of silica gel. The fractions eluted with benzene–ether (9:1) gave 661 mg of the hydroxyaldehyde **16** in a yield of 79%, which was recrystallized from acetone yielding a pure sample, mp 112–114°, $[\alpha]^{23}D$ +11.5 ± 0.6° (*c* 0.989). The infrared spectrum showed absorption of OH at 3524 and 3470 cm^{-1}, C=O at 2720, 1717, and 1706 cm^{-1}. The nmr spectrum showed τ 9.33 (s, 3 H of 13-CH_3), 9.09 (s, 3 H of 10-CH_3), 6.90–7.40 (broad m, 1 H of 2β-H), and 0.26 (d, J = 2.0 Hz, 1 H of CHO).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.56; H, 11.44.

5-Hydroxy-*A*-nor-5α-cholestane-2α-carboxylic Acid Lactone (17).—To a solution of 50 mg of **16** in 0.5 ml of acetone was added 0.05 ml of 8 *N* Jones reagent, and the mixture was stirred for 10 min at room temperature. The reaction solution was poured into ice–water and extracted with ether. The ether extract was washed with sodium carbonate, dried over sodium sulfate, and then evaporated to dryness giving 30 mg of **17** as colorless crystals in a yield of 60%. These were recrystallized from ether–methanol: mp 145–147°; $[\alpha]^{23}D$ 0 ± 0.4°; $[\alpha]_{436}$ −51.8 ± 4.0°; $[\alpha]_{365}$ −186.8° (*c* 0.985); CD (isooctane) $[\theta]_{255}$ 0, $[\theta]_{219}$ −14690, $[\theta]_{210}$ −9770; ORD (isooctane) $[\phi]_{235}$ −6765, $[\phi]_{207}$ +15650. The infrared spectrum showed an absorption of C=O at 1784 cm^{-1}. The nmr spectrum gave τ 9.18 (s, 3 H of 13-CH_3), 8.93 (s, 3 H of 10-CH_3), and 7.27 (m, 1 H of 25-H).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.87; H, 11.00.

Kinetic Measurements.—The dioxane was treated by the procedure of Fieser,[17] distilled from sodium, and stored under nitrogen. Perchloric acid standard solution was prepared by diluting 0.85 ml of reagent grade 70% perchloric acid with the above dioxane to 100 ml of the total volume, followed by further dilution fifty times with dioxane; the concentration was approximately 0.002 *N*. Samples of the mesylates and the bromides (*ca.* 0.08 mmol) were weighed into a 20-ml volumetric flask and dissolved with a constant volume of the dioxane, followed by addition of purified water containing 0.088 mmol of sodium acetate to the total volume of 20 ml. Aliquots, nine 2-ml portions, were pipetted from the flask into ampoules. The sealed ampoules were placed in the constant temperature bath and then plunged into 10 ml of the dioxane. In the case of **5**, aliquots were pipetted directly from the volumetric flask maintained at the reaction temperature into 10 ml of cooled acetone and titrated. "Infinity" ampoules were removed after ten half-lives and usually two were taken for each run. The sodium acetate decrease on the formation of methanesulfonic acid or hydrobromic acid was titrated with the standard perchloric acid solution using a Metrohm potentiograph E336. Rate constants were determined by the infinity titer method.

Registry No.—**5**, 28627-71-6; **6**, 28627-72-7; **7**, 28627-73-8; **8**, 27948-66-9; **9**, 26519-23-3; **10**, 27948-63-6; **12**, 28627-77-2; **13**, 28627-78-3; **14**, 28627-79-4; **15**, 28627-81-8; **16**, 28627-82-9; **17**, 28627-83-0.

(16) S. Winstein and D. Trifan, *J. Amer. Chem. Soc.*, **74**, 1147 (1952).

(17) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, Boston, Mass., 1957, p 284.

Reactions of *p*-Toluenesulfonyl Chloride and *p*-Toluenesulfonyl Cyanide with Sodium Cyanide and with Sodium *p*-Toluenesulfinate

FRED P. CORSON AND R. GARTH PEWS*[1]

Hydrocarbons and Monomers Research Laboratory, The Dow Chemical Company, Midland, Michigan 48640

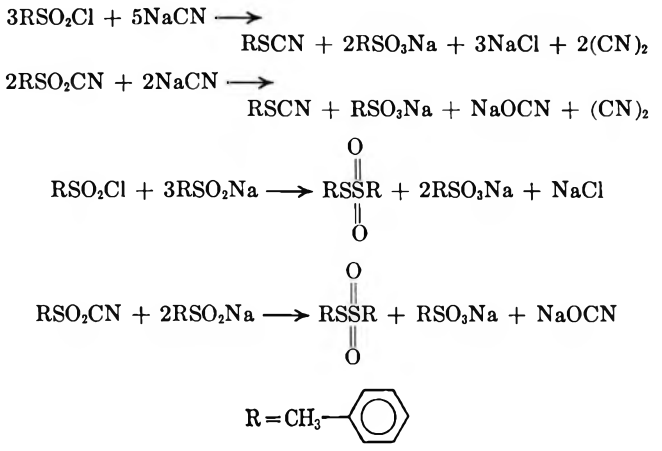
Received October 26, 1970

The reactions of *p*-toluenesulfonyl chloride and *p*-toluenesulfonyl cyanide with sodium cyanide and with sodium *p*-toluenesulfinate in acetonitrile at 70° were investigated. The stoichiometry and products of each reaction were shown in Scheme I.

The reactions of sulfonyl halides with inorganic cyanides have not been well documented. Van Leusen[2] recently stated that sulfonyl cyanides cannot be prepared by the reaction of sulfonyl chlorides with potassium, cuprous, silver, or lithium cyanides, but he did not report the actual course of the reaction. Loew[3] and McGowan[4] reported that reaction of trichloromethanesulfonyl chloride with potassium cyanide in water gave potassium trichloromethylsulfinate, cyanogen, and potassium chloride. Trichloromethanesulfonyl chloride, however, is not a representative sulfonyl halide.[5]

As part of a search for a facile synthesis of sulfonyl cyanides,[6] we investigated the reaction of *p*-toluenesulfonyl chloride (**1**) with sodium cyanide (**2**). As part of the effort to elucidate the mechanism of this reaction, we also investigated the reaction of **1** with sodium *p*-toluenesulfinate (**4**) and the reactions of *p*-toluenesulfonyl cyanide (**3**) with **2** and with **4**. The reactions of sulfonyl cyanides with **2** or **4** have not been previously reported (see Scheme I).

SCHEME I



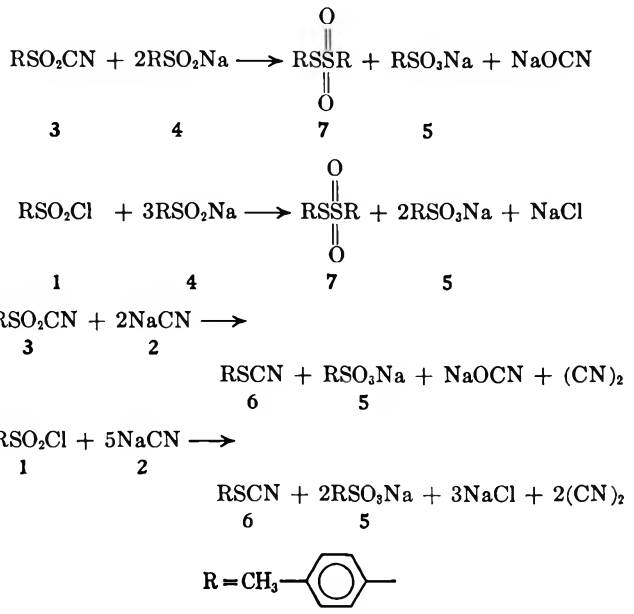
The reaction of sulfonyl chlorides with sulfinate salts has been reported to give α disulfones. Kohler and MacDonald[7] report isolation of 4,4′-dimethyldiphenyl disulfone from the reaction of **1** with **4** in mixed water–diethyl ether solvent. They give no yield data. Urushibara and Koga[8] report the isolation of a 4.3% yield of 4,4′-dimethyoxydiphenyl disulfone from the reaction of *p*-methoxybenzenesulfonyl chloride with sodium *p*-methoxybenzenesulfinate in mixed water–acetone solvent. No other products are described.

Results and Discussions

The reactions of **1** and **3** with **2** and **4** in acetonitrile at 70° were investigated. The products, product distributions, and stoichiometry of each reaction were determined. The results are described in Scheme II.

SCHEME II

STOICHIOMETRY OF REACTIONS



The reactions were followed by disappearance of starting **1** or **3** as determined by vpc. The reactions were complete as soon as **1** or **3** had disappeared. Work-up and analysis of reaction mixtures before **1** or **3** had completely disappeared resulted in product distributions identical with those at complete reaction. No other intermediates or products were detected. Therefore, **1** or **3** is involved in the slow step in each reaction. The relative rates of these reactions were $3 + 4 > 1 + 4 > 3 + 2 > 1 + 2$.

Postulated mechanisms for each of these reactions will be discussed. The faster reactions will be discussed first since they are logical intermediate steps in the slower reactions.

(1) To whom inquiries should be addressed: The Halogens Research Laboratory, The Dow Chemical Co., Midland, Mich.

(2) A. Van Leusen, A. Iedema, and J. Strating, *Chem. Commun.*, **18**, 440 (1968).

(3) O. Loew, *Bull. Soc. Chim. Fr.*, **11**, 486 (1869).

(4) G. McGowan, *J. Prakt. Chem.*, **19**, 456 (1896).

(5) N. Kharasch, *Org. Sulfur Compounds*, **1**, 371 (1961).

(6) Three independent syntheses of sulfonyl cyanides have now been published: (a) ref 2; (b) J. Cox and R. Ghosh, *Tetrahedron Lett.*, **39**, 3351 (1969); (c) R. G. Pews and F. P. Corson, *Chem. Commun.*, 1187 (1969).

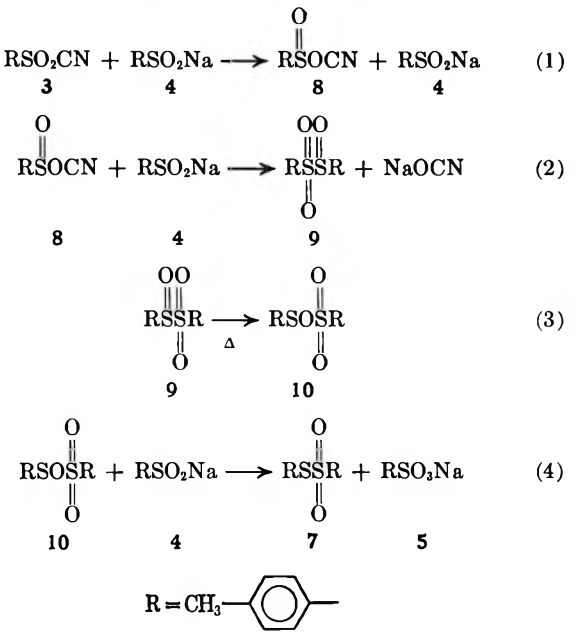
(7) E. Kohler and M. MacDonald, *Amer. Chem. J.*, **22**, 219 (1899).

(8) Y. Urushibara and G. Koga, *Nippon Kagaku Zasshi*, **81**, 1615 (1960).

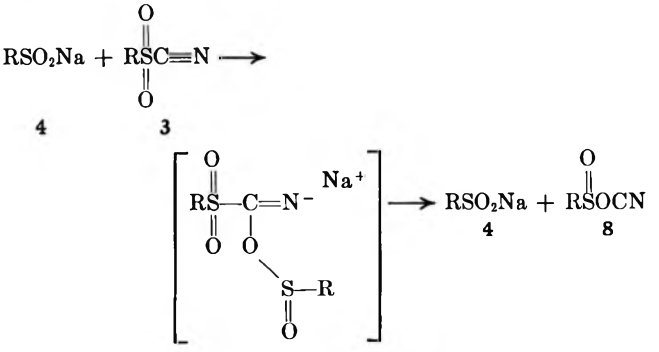
The postulated course of the reaction of **3** with 2 molar equiv of **4** to give 1 molar equiv each of sodium *p*-toluenesulfonate (**5**), *p*-tolyl *p*-toluenethiosulfonate (**7**), and sodium cyanate is described in Scheme III.

Scheme III

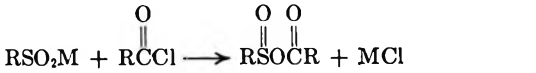
Reaction of *p*-Toluenesulfonyl Cyanide with Sodium *p*-Toluenesulfinate



Each of the reactions 1 through 4 has precedent or analogy in the literature. Van Leusen[9] has reported the reaction of **3** with a wide variety of nucleophiles including phenoxide, hydroxide, and thiophenoxide, all of which attacked at the cyanocarbon to displace the sulfinate and transfer the cyano group to the nucleophile. Reaction 1 would be expected to occur by the same mechanism. Attack by sulfinate sulfur would simply regenerate **3** and **4**. Attack by the sulfinate oxygen would give the sulfinyl cyanate **8**.

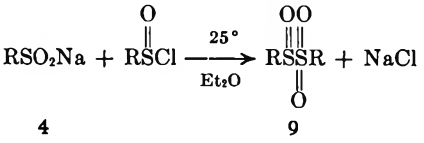


Precedent exists for nucleophile attack by the sulfinate oxygen at the unsaturated carbon, albeit the carbonyl rather than the cyano carbon. Reaction of metal sulfinates with acid chlorides has been shown to give mixed anhydrides by O-acylation.[10,11]



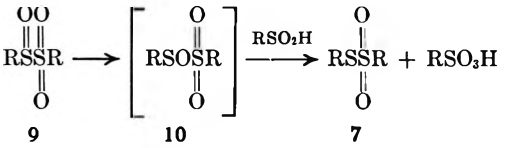
(9) A. Van Leusen and J. Jagt, *Tetrahedron Lett.*, **12**, 967 (1970).
(10) H. Böhme and K. Meyer-Dulheuer, *Justus Liebigs Ann. Chem.*, **688**, 78 (1965).
(11) M. Kobayashi, *Bull. Soc. Chem. Jap.*, **39**, 967 (1966).

Nucleophilic attack of **4** on the sulfinyl sulfur of **8** would be expected to occur with sulfur as one nucleophile to give the *p*-toluenesulfinyl *p*-toluenesulfone (**9**) and sodium cyanate (reaction 2, Scheme III). Kice and coworkers[12] have shown sulfinyl sulfur to be a soft electrophilic center in the HSAB[13,14] nomenclature and more readily attacked by soft nucleophiles such as iodide and thiocyanate than by hard nucleophiles such as acetate. In addition, the reaction of **4** with *p*-toluenesulfinyl chloride has been shown to give **9**.[15]



Attack by the sulfinate oxygen of **4** at the cyanate carbon of **8** would simply regenerate **4** and **8**. Attack by the sulfinate sulfur at the cyanate carbon would regenerate **4** and **3**.

The thermal decomposition of **9** has been well documented by Kice and coworkers.[16] It occurred in acetonitrile at 50° with a first-order rate constant of 5.4×10^{-4} sec^{-1}.[16] The initially formed intermediate **10** was shown to react with *p*-toluenesulfinic acid to give *p*-tolyl *p*-toluenethiosulfonate (**7**) and *p*-toluenesulfonic acid.[16] On this basis, the **9** formed in the reaction of **8**



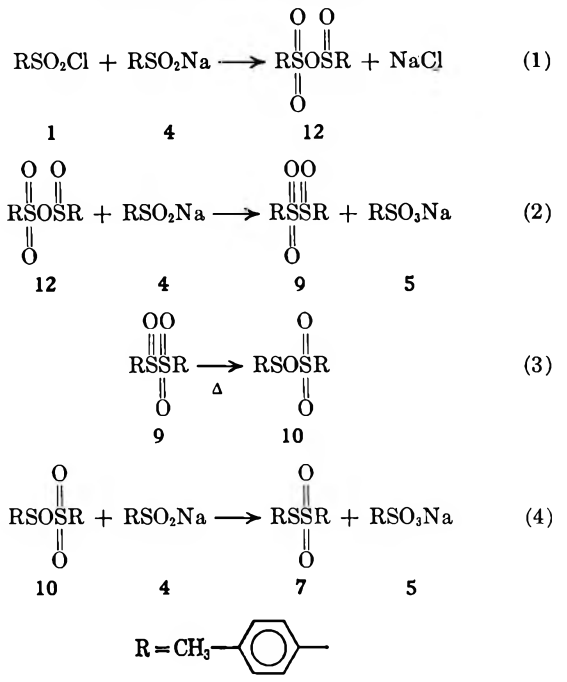
with **4** would be expected to undergo isomerization to **10** (reaction 3, Scheme III) at 70° in acetonitrile. Reaction of **10** with **4** would give the final sulfur-containing products **7** and **5** (reaction 4, Scheme III). The nucleophilic attack on the sulfenyl sulfur of **10** by the sulfur of **4** or of *p*-toluenesulfinic acid is expected. Kice and coworkers[12,17] have shown that sulfenyl sulfur is a softer electrophilic center than even sulfinyl sulfur. Nucleophilic attack of **4** on **9**, if it competes with isomerization to **10**, would be expected to occur at the sulfinyl sulfur by the sulfinate sulfur to simply regenerate **4** and **9**. It is well known that the electrophilicity of sulfur increases rapidly in the order sulfonyl < sulfinyl < sulfenyl.[18]

The reaction of **1** with 3 mol of **4** gave 2 mol of **5**, 1 mol of **7**, and 1 mol of sodium chloride. These products could arise *via* initial attack of the sulfinate oxygen of **4** at either sulfur (Scheme IV) or chlorine (Scheme V) of **1**. Attack by the sulfinate sulfur at chlorine would regenerate **1** and **4**. Attack by the sulfinate sulfur at sulfur would produce 4,4′-dimethyldiphenyl disulfone (**11**) which is observed in 4% yield. This is in agreement with the results of Urushibara and Koga described earlier.[8] A control experiment showed that **11** does not react further with **4** under the reaction conditions.

(12) J. Kice and G. Guaraldi, *J. Amer. Chem. Soc.*, **90**, 4076 (1968).
(13) R. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).
(14) R. Pearson, *ibid.*, **85**, 3533 (1963).
(15) H. Bredereck, A. Wagner, H. Beck, and R. Klein, *Ber.*, **93**, 2736 (1960).
(16) J. Kice and N. Pawlowski, *J. Amer. Chem. Soc.*, **86**, 4898 (1964).
(17) J. Kice and G. Large, *ibid.*, **90**, 4069 (1968).
(18) See the data in ref 12 and 17.

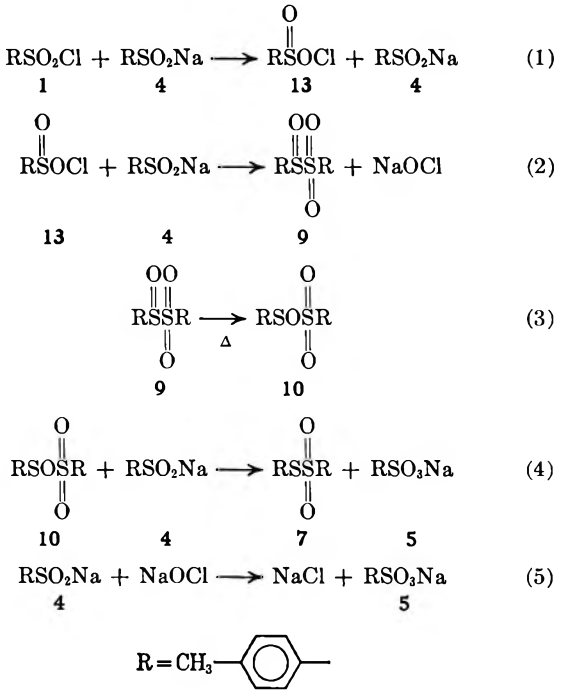
SCHEME IV

REACTION OF *p*-TOLUENESULFONYL CHLORIDE WITH SODIUM *p*-TOLUENESULFINATE. INITIAL ATTACK AT SULFUR



SCHEME V

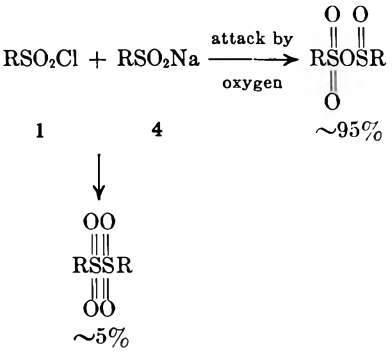
REACTION OF *p*-TOLUENESULFONYL CHLORIDE WITH SODIUM *p*-TOLUENESULFINATE. INITIAL ATTACK AT CHLORINE



There is no precedent in the literature for attack of an oxygen nucleophile at the chlorine of **1** (reaction 1, Scheme V). Reaction of **1** with alkoxides or phenoxides[19] gives sulfonate esters and with hydroxide[20] gives *p*-toluenesulfonic acid. In addition, control experiments showed that sodium hypochlorite (reaction 2, Scheme V) was not present in the reaction mixture. Oxidation of a mixture of 0.1 mol each of **4** and β-methyl naphthyl ketone in acetonitrile at 70° by dropwise addition of Clorox (0.07 mol of sodium hypochlorite total) gave 11% conversion of the β-methyl naphthyl ketone to β-naphthoic acid. Reaction of **1** with **4** in the presence of β-methyl naphthyl ketone gave no conversion to β-naphthoic acid and did not alter the course of the reaction. On the basis of this evidence, Scheme V is eliminated and Scheme IV is postulated as the major reaction pathway.

Attack by the sulfinate oxygen of **4** at the sulfonyl sulfur of **1** (reaction 1, Scheme IV) would give the sulfinyl sulfonyl anhydride **12** and sodium chloride. Reaction of **12** with **4** to give **9** and **5** (reaction 2, Scheme IV) is analogous to the reaction of **4** with the sulfinyl cyanate **8** previously discussed (reaction 2, Scheme III), the only difference being the leaving group is sulfonate rather than cyanate. The rearrangement of **9** to **10** and the reaction of **10** with **4** to give the final products (reactions 3 and 4, Scheme IV) are identical to reactions 3 and 4, Scheme III.

Thus, reaction of **1** with **4** appears to occur completely by attack at the sulfonyl sulfur, about 95% of the attack occurring by the sulfinate oxygen. This preferential attack by oxygen is compatible with the data obtained by Kice and coworkers[12] which indicates that sulfonyl sulfur is a much harder electrophilic center than sulfinyl sulfur and more readily attacked by hard nucleophiles such as acetate and fluoride than by soft nucleophiles such as bromide and thiocyanate.



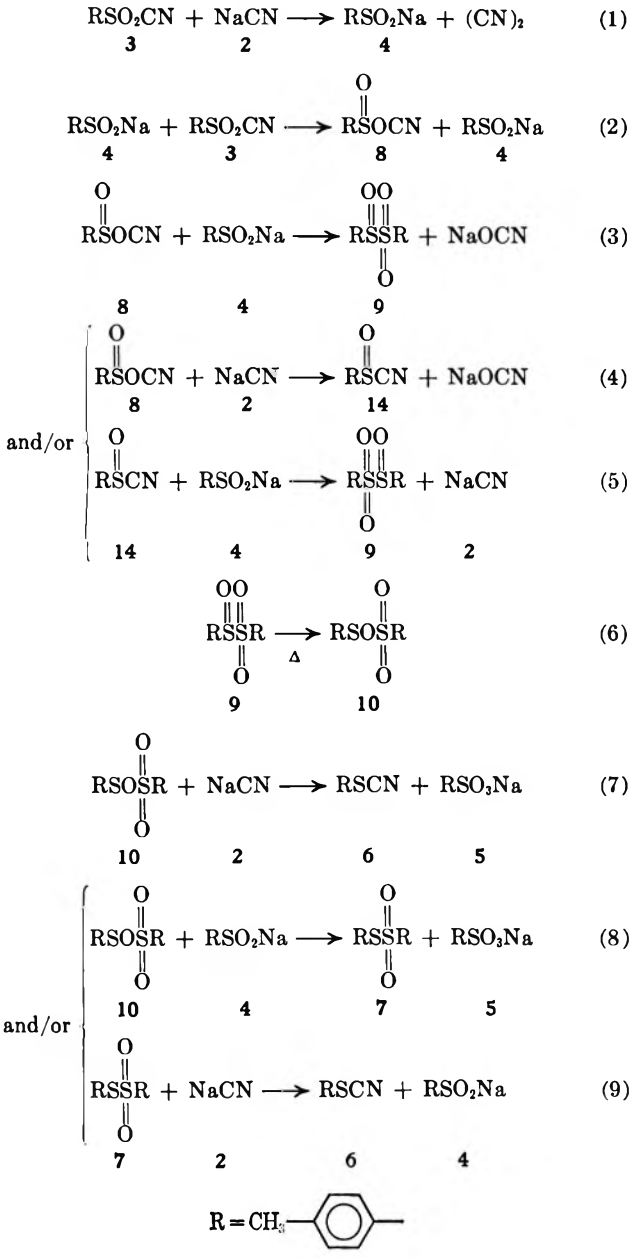
The postulated course of the reaction of **3** with 1 mol of sodium cyanide (**2**) to give 0.5 mol each of **5**, 4-thiocyanotoluene (**6**), cyanogen, and sodium cyanate is outlined in Scheme VI. Reactions 2, 3, 6, and 8 are identical with reactions already described.

As previously discussed, initial nucleophilic attack on **3** is expected at cyanocarbon. Reaction of **2** would give **4** and cyanogen (reaction 1, Scheme VI). Reaction of **4** with **3** to give **8** (reaction 2, Scheme VI) has already been discussed. The reaction of **4** with **3** must be significantly faster than the reaction of **2** with **3**, or the isolated products would be **4** and cyanogen. A control experiment showed that **4** will not react with cyanogen under the reaction conditions. The only information obtained on the relative rates of these reactions is that the reaction of **3** with **4** is complete in 3 hr at 70° while the reaction of **3** with **2** requires 10 hr at 70°.

Nucleophilic attack on **8** by **4** to give **9** (reaction 3, Scheme VI) has been discussed. Attack by **2** would be expected to give the sulfinyl cyanide **14** and sodium cyanate (reaction 4, Scheme VI). Reaction of **14** with

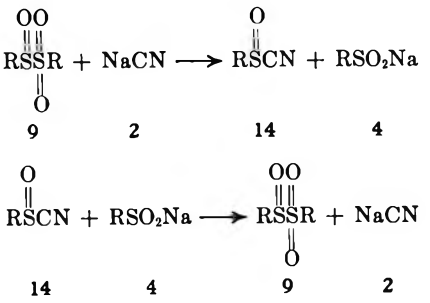
(19) J. Bunnett, *Adv. Phys. Org. Chem.*, **2**, 271 (1963).
(20) C. Suter, "Organic Chemistry of Sulfur Compounds," Wiley, London, 1944, p 497.

Scheme VI
Reaction of p-Toluenesulfonyl Cyanide with Sodium Cyanide



4 could lead to 9 and regenerate 2 (reaction 5, Scheme VI). The overall result of reactions 4 and 5 is identical with that of reaction 3.

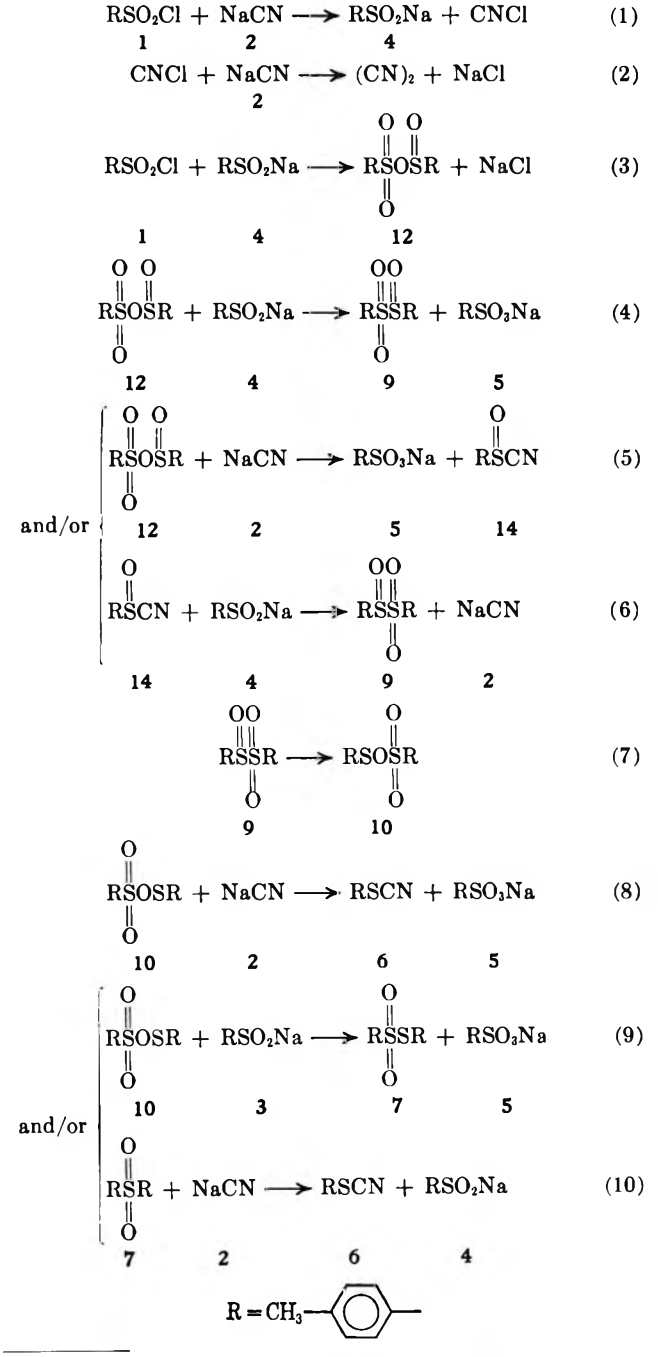
Isomerization of 9 to 10 might be in competition with nucleophilic attack on 9. As discussed previously, attack by 4 would simply regenerate 4 and 9. Attack by cyanide would be expected to also lead to regeneration of 9 in two steps.



The intermediate 10 can undergo nucleophilic attack at the sulfenyl sulfur by either 2 or 4. Attack by 2 (reaction 7, Scheme VI) would give the stable products 6 and 5. Reaction with 4 (reaction 8, Scheme VI), as discussed previously (reaction 4, Scheme II and reaction 4, Scheme III), would give 7 and 5. 7 should react with 2 to give the stable product 6 and regenerate 4 (reaction 9, Scheme VI). The overall result of reactions 8 and 9 would be identical with that of reaction 7. The reaction of the S esters of thiolsulfonic acids with cyanide is known to give thiocyanates and sulfinates.[21]

The postulated course of the reaction of 3 mol of 1 with 5 mol of 2 to give 2 mol each of cyanogen and 5, 1 mol of 6, and 3 mol of sodium chloride is outlined in Scheme VII. Reactions 3, 4, 6–9, and 10 are identical

Scheme VII
Reaction of p-Toluenesulfonyl Chloride with Sodium Cyanide



(21) R. Otto and A. Rossing, *Chem. Ber.*, **20**, 2079 (1887).

with reactions already discussed. The only reactions which do not follow directly from previous discussion are 1, 2, and 5.

As discussed for the reaction of **1** with **4**, hard nucleophiles have been shown to react with **1** at sulfur. In contrast, soft nucleophiles such as amines, mercaptides, and carbanions have been shown to react with **1** to give products best explained as occurring *via* initial attack at chlorine.[19] On this basis, cyanide would be expected to attack **1** at chlorine to give **4** and cyanogen chloride (reaction 1, Scheme VII). Attack by the cyanide at the sulfur of **1** would give the sulfonyl cyanide **3** which has been shown to react with the cyanide ion to give sodium cyanate, which was not observed in this reaction.

The reaction of **1** with **4** to give **12** (reaction 3, Scheme VI) must be fast compared to initial reaction of **1** with **2**, just as the reaction of **3** with **4** must be fast compared to reaction of **3** with **2** (reactions 1 and 2, Scheme VI). Likewise, reaction of cyanogen chloride with cyanide to give cyanogen must be fast compared with reaction with **4** to give **3**. The latter reaction would eventually lead to sodium cyanate. Unfortunately, there appear to be no obvious reasons why these relative rates should prevail.

The remaining reactions leading to products have already been discussed except for reaction 5, Scheme VII. Attack of the cyanide on **12** would be expected to occur at the sulfinyl sulfur to give the already described sulfinyl cyanide **14**.

In conclusion, the courses of the reactions of **1** and **3** with **2** and with **4** have been determined. Mechanisms have been proposed and supported which are internally consistent and consistent with the many pertinent facts in the literature: attack of hard nucleophiles at the sulfur of **1**;[19,20] attack of soft nucleophiles at the chlorine of **1**;[19] attack by a large variety of nucleophiles at the cyanocarbon of **3**;[9] increasingly hard electrophilicity of the sulfur in the order sulfenyl < sulfinyl < sulfonyl;[12,17] the very low yield of the disulfones in the reaction of sulfinates with sulfonyl chlorides.[7,8] The original question of why reactions of sulfonyl halides with cyanide ion do not give sulfonyl cyanides has been answered. Further evidence has been provided that application of the HSAB concept is a useful tool in predicting, or at least explaining, the course of many ionic reactions at sulfur.

Experimental Section

p-Toluenesulfonyl chloride (**1**) Aldrich Chemical Co., was recrystallized. Sodium cyanide (**2**) was Fisher Scientific Co. reagent grade. Sodium *p*-toluenesulfinate (**4**) was prepared exactly as described by Field and Clark.[22] Acetonitrile, Burdick and Jackson Laboratories, Inc., was distilled over calcium hydride. Cyanogen chloride was obtained from American Cyanamide.

Reaction of *p*-Toluenesulfonyl Chloride (1) with Sodium Cyanide (2).[23]—A mixture of **1** (45.3 g, 0.25 mol) and **2** (24.5 g, 0.50 mol) in acetonitrile (500 ml) in a 1-l., three-necked flask equipped with a reflux condenser leading to a CO_2–acetone cooled trap, a mechanical stirrer, and a nitrogen inlet tube was stirred at 70° for 20 hr. Vpc analysis indicated complete reaction of **1**. The reaction mixture was filtered to give a solid residue, 29.4 g. The acetonitrile was removed from the filtrate to give a residue, 29.8 g. The combined residues were extracted with two 200-ml portions of hot benzene. The benzene was removed by distillation and the residue distilled giving 10.1 g (27.1% based on **1**) of 4-thiocyanotoluene (**6**): bp 77° (0.8 mm) [lit.[24] bp 155–158° (40–50 mm)]; ir (CCl_4) 2170 (SC≡N).

Anal. Calcd for C_8H_7NS: C, 64.43; H, 4.70; N, 9.40. Found: C, 64.41; H, 4.81; N, 9.43.

The residue from the benzene extraction was extracted with two 200-ml portions of methanol. The methanol was removed to give 30.7 g (62% based on **1**) of sodium *p*-toluenesulfonate (**5**); the ir, nmr, and mass spectral data were identical with those of an authentic sample obtained from Matheson Coleman and Bell. The residue from the methanol extraction weighed 15.1 g. Standard Volhard potentiometric titration showed it to contain 78% NaCl (11.9 g, 0.21 mol, 84% based on **1**); ir (Fluorolube) 2085 cm^{-1} (weak, presence of NaCN), no absorption at 2150–2200 cm^{-1} (no NaOCN).

The liquid trapped in the CO_2–acetone cooled trap weighed 11.1 g. Mass spectral analysis showed the presence of cyanogen (73%, 8.1 g, 0.155 mol, 0.62 mol/mol of **1**), N_2, acetonitrile, and CO_2.

Exact repetition of the reaction using a 1:1 mol ratio of **1** to **2** gave the same products in the same proportion with unreacted **1**. Reaction for 20 hr at 70° using a 3:5 mol ratio of **1** to **2** gave complete conversion of both starting materials. Reaction with a 3:5 mol ratio for 10 hr at 70° gave the same product distribution with unreacted **1**.

Preparation of *p*-Toluenesulfonyl Cyanide (3).[25]—Cyanogen chloride (70.0 g, 1.14 mol) was bubbled into a slurry of sodium *p*-toluenesulfinate (167.0 g, 0.94 mol) in acetonitrile (1 l.) in a flask equipped with CO_2–acetone cooled condenser with a calcium chloride drying tube, mechanical stirrer, and gas inlet tube. The mixture was stirred for 1 hr at 25° and filtered, and the solvent was removed on a rotary evaporator. The resulting solid was recrystallized from hexane to give 131.6 g (77%) of **3**: mp 47–48° (lit.[4] mp 49–50°); bp 105–106°; ir (film) 2194 (C≡N) and 1375 and 1173 cm^{-1} (SO_2); nmr (CCl_4) δ 7.93 (m, 2), 7.49 (m, 2), and 2.52 (m, 3); mass spectrum (decreasing intensity) *m/e* 91, 181, 155, and 65.

Anal. Calcd for C_8H_7NOS: C, 53.04; H, 3.87; N, 7.73. Found: C, 53.20; H, 4.09; N, 7.72.

Reaction of *p*-Toluenesulfonyl Cyanide (3) with Sodium Cyanide (2).—A mixture of **3** (45.3 g, 0.25 mol) and **2** (12.3 g, 0.25 mol) in acetonitrile (500 ml) in the equipment described above for the reaction of **1** with **2** was heated at 70° for 10 hr. Vpc indicated complete reaction of **3**. The reaction mixture was worked up and analyzed exactly as described above to give the following products (per cent yields based on **3**): **6** (16.4 g, 44%), **5** (23.3 g, 48%), cyanogen (5.7 g, 44%), sodium cyanate (7.8 g, 48%). Reaction for 5 hr at 70° gave the same product distribution with recovered **3**.

Reaction of *p*-Toluenesulfonyl Chloride (1) with Sodium *p*-Toluenesulfinate (4).—A mixture of **1** (19.05 g, 0.1 mol) and **4** (53.4 g, 0.3 mol) in acetonitrile (600 ml) was stirred under nitrogen at 70° for 5 hr. The reaction mixture was cooled to 25° and filtered to give 46.0 g of white solid. Standard Volhard potentiometric filtration showed the presence of 12.4% sodium chloride (5.7 g, 97% based on **1**). The ir and nmr spectra of this solid were identical with those of the authentic sample of **5** (assuming only sodium chloride and **5** to be present, 40.3 g, 210% based on **1**).

The acetonitrile filtrate was cooled to 0° overnight. The resulting white crystals were collected and dried to give 1.5 g (4.8% based on **1**) of 4,4-dimethyldiphenyl disulfone (**11**): mp 208–210° (lit.[26] mp 211°); ir (CS_2) 1335 and 1135 cm^{-1} (SO_2); nmr (CD_3CN) δ 7.45 (m, 2), 7.65 (m, 2), and 2.47 (s, 3); mass spectrum *m/e* 310, 262, 246, 155, 139, and 91.

Anal. Calcd for $C_{14}H_{14}O_4S_2$: C, 54.19; H, 4.52; S, 20.65. Found: C, 54.23; H, 4.49; S, 20.61.

The acetonitrile was removed from the filtrate by distillation to give a white, crystalline solid, which was recrystallized from hexane to give 20.4 g (73% based on **1**) of *p*-tolyl *p*-toluenethiosulfonate (**7**): mp 77–78° (lit.[27] mp 77–78°); ir (CS_2) 1335 and

(22) L. Field and R. Clark, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 674.

(23) Observation of 4-thiocyanotoluene in this reaction was initially made by E. B. Nyquist in this laboratory.

(24) C. Rabaut, *Bull. Soc. Chim. Fr.*, **27**, 690 (1902).

(25) This preparation, discovered independently, is very similar to that described in ref 6b.

(26) H. Gilman, L. Smith, and H. Parker, *J. Amer. Chem. Soc.*, **47**, 860 (1925).

(27) J. Carson and F. Wong, *J. Org. Chem.*, **26**, 3028 (1961).

1148 cm^{-1} (SO_2); nmr (CCl_4) δ 7.2 (m, 8), 2.4 (s, 3), and 2.3 (s, 3); mass spectrum *m/e* 278, 214, 155, 139, 123, and 91.

Anal. Calcd for $C_{14}H_{14}O_2S_2$: C, 60.43; H, 5.04; S, 23.02. Found: C, 60.43; H, 4.98; S, 23.11.

Exact repetion of the reaction with a 1:2 mol ratio of 1 to 4 gave the same products in the same proportions with recovered 1. Reaction with a 1:3 mol ratio for 3 hr at 70° gave the same product distribution with unreacted 7.

Reaction of *p*-Toluenesulfonyl Cyanide (3) with Sodium *p*-Toluenesulfinate (4).—A mixture of 3 (18.1 g, 0.1 mol) and 4 (35.6 g, 0.2 mol) in acetonitrile (600 ml) was stirred under nitrogen at 70° for 3 hr. The reaction mixture was cooled to 25° and filtered. The rsulting solid residue was extracted with two 100-ml portions of methanol and the methanol removed to give 19.7 g (94% based on 3) of sodium *p*-toluenesulfonate (5); properties exactly as described above. The residue from the methanol extraction had an ir spectrum identical with that of sodium cyanate (5.9 g, 91% based on 3).

The acetonitrile filtrate was cooled to 0° overnight. There were no crystals formed. The acetonitrile was removed by distillation. The resulting solid was recrystallized from hexane to give 24.7 g (89% based on 3) of *p*-tolyl *p*-toluenethiosulfonate (7); properties exactly as described above.

Reaction of a 1:3 mol ratio of 3 to 4 resulted in formation of the same products in the same yields with recovery of unreacted 4. Reaction of a 1:2 mol ratio for 2 hr at 70° gave the same product distribution with recovered 3.

Reaction of Sodium Hypochlorite with Sodium *p*-Toluenesulfinate (4) and β-Methyl Naphthyl Ketone.—To a mixture of 4 (17.8 g, 0.1 mol) and β-methyl naphthyl ketone (Eastman Organic Chemicals, 17.0 g, 0.1 mol) maintained at 70° in acetonitrile (500 ml) was added dropwise over 2 hr Clorox (100 g of solution, 5.25 g NaOCl, 0.07 mol). The white solid residue was collected by filtration and dried to give 18.1 g of solid. Ir and nmr showed this to be a mixture of sodium *p*-toluenesulfinate (4) and sodium *p*-toluenesulfonate (5). No attempt was made at quantitative analysis.

The acetonitrile was removed from the filtrate. The residue (17.3 g) was dissolved in 100 ml of hot 95% ethanol. Standing overnight at 25° resulted in formation of 1.3 g (11% based on NaOCl) of β-naphthoic acid, mp 182–184° (lit.[28] mp 183–184°). The ir and nmr spectra were identical with those of an authentic sample from Eastman.

Reaction of *p*-Toluenesulfonyl Chloride (1) with Sodium *p*-Toluenesulfinate (4) in the Presence of β-Methyl Naphthyl Ketone.—The reaction of 1 and 4 (1:3 mol ratio) was carried out exactly as described above except for the presence of β-methyl naphthyl ketone (17.0 g, 0.1 mol). The reaction mixture was worked up exactly as described above to give, from the residue, sodium chloride (5.6 g, 96%) and sodium *p*-toluenesulfonate (39.3 g, 195%), and, from the filtrate, *p*-tolyl *p*-toluenethiosulfonate (20.6 g, 74%) and β-methyl naphthyl ketone (16.7 g, 98% recovery). There was no evidence for the presence of β-naphthoic acid.

Attempted Reaction of Sodium *p*-Toluenesulfinate (4) with 4,4′-Dimethyldiphenyl Disulfone (11).—A mixture of 4 (1.78 g, 0.01 mol) and 11 (1.40 g, 0.0045 mol, isolated from reaction of 1 with 4) in acetonitrile (100 ml) was heated at 70° for 10 hr. The reaction mixture was cooled and filtered to give 1.68 g (95% recovery) of 4. The filtrate was concentrated to 50 ml and cooled to 0° overnight. The resulting crystals were collected and dried to give 1.29 g (92% recovery) of 11.

Attempted Reaction of Sodium *p*-Toluenesulfinate (4) with Cyanogen.—A sealed glass ampoule containing 4 (1.78 g, 0.01 mol) and cyanogen (0.52 g, 0.01 mol) in acetronitrile (10 g) was heated at 70° for 8 hr. The cyanogen and acetronitrile were removed to give 1.69 g (95% recovery) of 4.

Registry No.—1, 98-59-9; 2, 143-33-9; 3, 19158-51-1; 4, 824-79-3.

(28) M. Newman and H. Holmes, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 428.

The Reactivity of Some Imide and Sulfonamide Anions with Methyl Iodide in Methanol[1]

J. F. BUNNETT*[2] AND JOHN H. BEALE

Metcalf Chemical Laboratories, Brown University, Providence, Rhode Island 02912

Received September 17, 1970

Rate coefficients for reactions of the anions of succinimide phthalimide, benzenesulfonamide, *N*-methylbenzenesulfonamide, and *N*-phenylbenzenesulfonamide and of methoxide ion with CH_3I in CH_3OH have been determined. Reactivity among the nitranion nucleophiles correlates with basicity, except that the benzenesulfonamide anion is about one-third as reactive as expected from its basicity.

Although the conjugate base anions of phthalimide, of succinimide, and of sulfonamides with at least one hydrogen on nitrogen are well known to be alkylated readily, the reactivity of such anions toward saturated carbon appears not previously to have been measured.

We have determined rates of reactions of the anions of succinimide, phthalimide, benzenesulfonamide, *N*-methylbenzenesulfonamide, and *N*-phenylbenzenesulfonamide with methyl iodide in methanol. Rates were determined by potentiometric titration of the iodide ion released. For reasons mentioned below, the rate of reaction of $NaOCH_3$ with CH_3I was also determined. Results are summarized in Table I.

When the amide or imide is quite acidic and the reactivity of its anion toward CH_3I is quite high compared to that of methoxide ion, such a study is straightforward. However, when these conditions are not met there is a complication stemming from incompleteness of conversion of the amide or imide to its conjugate base. The pertinent acid–base equilibrium is that of eq 1, in which "NH" represents the amide or imide and "N^-" its conjugate base.

$$CH_3O^- + NH \underset{}{\overset{K_{eq}}{\rightleftharpoons}} N^- + CH_3OH \qquad (1)$$

The total rate of displacement of the iodide ion is the sum of components due to CH_3O^- and to the nitranion nucleophile, N^-. When the amide or imide is furnished in excess over $NaOCH_3$, we may write eq 2 and 3, where $[CH_3O^-]_{st} = [CH_3O^-] + [N^-]$.

$$d[I^-]/dt = k_2[CH_3I][CH_3O^-]_{st} \qquad (2)$$

$$= k_N[CH_3I][N^-] + k_0[CH_3I][CH_3O^-] \qquad (3)$$

By equating the right sides of eq 2 and 3 and substituting for $[N^-]$ the product $K_{eq}[NH][CH_3O^-]$ (*cf.* eq 1), one obtains eq 4. Inasmuch as $[CH_3O^-]_{st} = (1 +$

$$k_2[CH_3O^-]_{st} = (k_N K_{eq}[NH] + k_0)[CH_3O^-] \qquad (4)$$

(1) Based on the Ph.D. Thesis of J. H. Beale, Brown University, 1966. This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society.

(2) University of California, Santa Cruz, California 95060.

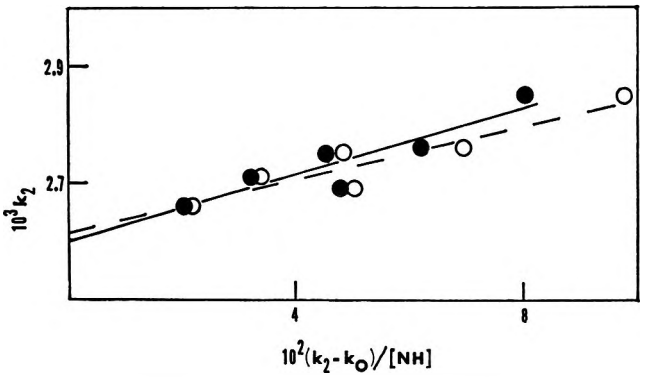


Figure 1.—Plots of data for the reaction of the benzenesulfonamide anion with CH_3I at 52.6°, according to eq 5. Open circles and broken line, first plot; filled circles and solid line, iteration.

TABLE I

REACTIONS OF IMIDE AND SULFONAMIDE ANIONS WITH METHYL IODIDE IN METHANOL

Nucleophile	Temp, °C	k_N, M^{-1} sec^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal deg^{-1} mol^{-1}
$C_6H_5SO_2NCH_3^-$ [a]	25.0	(1.01×10^{-3}) [b]		
	30.0	1.68×10^{-3}	17.8	−10.3
	59.9	2.64×10^{-2}		
Succinimide anion	25.0	(3.74×10^{-4}) [b]		
	30.0	6.25×10^{-4} [c]	18.0	−11.8
	59.9	9.89×10^{-3} [e]		
Phthalimide anion	25.0	(3.01×10^{-4}) [b]		
	30.0	5.11×10^{-4} [d]	18.6	−10.1
	59.9	9.10×10^{-3} [e]		
$C_6H_5SO_2NH^-$ [a]	25.0	(1.70×10^{-4}) [b]		
	30.0	2.82×10^{-4}	18.4 ± 0.3	−12.1
	40.6	8.50×10^{-4}		
	52.6	2.61×10^{-3}		
	59.9	4.70×10^{-3}		
$C_6H_5SO_2NC_6H_5^-$	25.0	(1.10×10^{-4}) [b]		
	30.0	1.92×10^{-4} [d]	19.7	−8.5
	59.9	3.98×10^{-3} [e]		
$NaOCH_3$	25.0	(2.60×10^{-4}) [b]		
	30.0	4.68×10^{-4}	20.9 ± 0.6	−2.6
	40.6	1.64×10^{-3}		
	52.6	5.23×10^{-3}		
	59.9	1.21×10^{-2}		

[a] See text for method of treating kinetic data. [b] Extrapolated value. [c] Average of two runs. [d] Average of three runs. [e] Average of four runs.

$K_{eq}[NH])[CH_3O^-]$, further substitution and rearrangement afford[3] eq 5.

$$k_2 = k_N + \frac{k_0 - k_2}{K_{eq}[NH]} \quad (5)$$

According to eq 5, a plot of the observed second-order rate coefficient, k_2, against $(k_0 - k_2)/[NH]$ should be linear with slope $1/K_{eq}$ and intercept k_N. Use of such a plot ot evaluate k_N requires, however, that one know k_0 and [NH]. The former is the rate coefficient for reaction of CH_3O^- with CH_3I and is easily determined separately. The value of [NH] depends on K_{eq} which itself is learned from the slope of the plot. Accordingly, a procedure of iteration was used; it was initially assumed that the only NH present was that in excess of the $NaOCH_3$ added, that is, that reaction 1 had gone to completion. K_{eq} was then estimated from the slope of a plot according to eq 5 and used to reckon a value of [NH] for each reaction mixture. The cycle was repeated until further iteration did not appreciably affect the slope or intercept.

(3) *Cf.* J. F. Bunnett and L. A. Retallick, *J. Amer. Chem. Soc.*, **89**, 423 (1967).

Experiments at several concentrations of excess amide or imide showed that succinimide, phthalimide, and *N*-phenylbenzenesulfonamide are acidic enough so that equilibrium 1 lies essentially fully to the right if excess amide or imide is employed. In these cases k_2 as measured could be equated directly with k_N. With benzenesulfonamide, two cycles of application of eq 5 were sufficient; the first and second cycle plots at 52.6° are presented for purposes of illustration in Figure 1. The k_N values resulting from this treatment of data at four temperatures are listed in Table I; the K_{eq} values varied irregularly with temperature between 164 and 349 M^{-1}. With *N*-methylbenzenesulfonamide, three cycles of application of eq 5 were necessary; the resulting k_N appear in Table I; the K_{eq} from the third cycle were 12 M^{-1} at 30° and 16 M^{-1} at 60°.

Rate coefficients for all runs and details on treatment of them according to eq 5 are given in the thesis of Beale.[1]

In Table I, it is to be noted that the rate coefficients for the nitranion[4] nucleophiles differ at most by a factor of ten and that the reactivity of methoxide ion falls within the range of the nitranion nucleophiles. Entropies of activation are nearly constant among the nitranions, and with one possible exception their rank in reactivity is consistent with their respective enthalpies of activation. The entropy of activation for methoxide ion is distinctly higher than for the nitranions.

For the several nitranions, pK_a's in methanol were estimated in several ways: by conductimetric studies in methanol (on solutions made by combining $NaOCH_3$ and the various NH species in various ratios), from the slopes of the aforementioned plots according to eq 5, by adding 3.9 to pK_a's in 50% (w/w) aqueous methanol determined by potentiometric titration with a glass electrode,[5] and by adding 5.0 to pK_a's in water from the literature.[6] Details are given in the Ph.D. thesis of Beale.[1] For any amide or imide, the several estimates were in fair to good agreement with each other. The pK_a's estimated for anhydrous methanol (with average deviations among the estimates) were as follows: *N*-methylbenzenesulfonamide, 15.5 ± 0.3; succinimide, 14.1 ± 0.3; phthalimide, 14.5 ± 0.5; benzenesulfonamide, 14.9 ± 0.1; and *N*-phenylbenzenesulfonamide, 13.3.

The relationship of nucleophilicity to basicity within this series is shown by a plot (Figure 2) of log k_N (at 30°) *vs.* pK_a. The plot is somewhat arbitrary owing to uncertainty in some of the pK_a estimates. The line drawn is based on linear regression analysis of the data plotted except that for benzenesulfonamide ion. The slope, β', is 0.4. With the usual reservation,[7] this β' value suggests that the forming N–C bond is less than half formed at the transition state.

The point in Figure 2 for the benzenesulfonamide ion falls below the line defined by the other nitranions by 0.52 log units, equivalent to a factor of 3.3 in re-

(4) The term "nitranion" represents an anion with negative charge significantly (but not necessarily exclusively) on nitrogen. It is analogous to the terms "oxyanion" and "carbanion."

(5) M. Paabo, R. A. Robinson, and R. G. Bates, *J. Amer. Chem. Soc.*, **87**, 415 (1965).

(6) A. L. Bacanella, E. Grunwald, H. P. Marshall, and E. L. Purlee, *J. Org. Chem.*, **20**, 747 (1955).

(7) J. F. Bunnett, *Ann. Rev. Phys. Chem.*, **14**, 271 (1963).

activity. The diminished reactivity of benzenesulfonamide anion is reminiscent of discrepancies often observed in similar Brønsted-like plots for hydroxide ion as compared to alkoxide ions or of ammonia as compared to amines.

The autoprotolysis constant for methanol, as pK_s, is 16.9,[8] and pK_a by the usual arbitrary conversion is 18.3. Extrapolation of the line in Figure 2 would lead to a log k_N at pK_a 18.3 some 1.7 log units greater than observed for methoxide ion, equivalent to a 50-fold deficiency in reactivity for this oxyanion nucleophile.

Experimental Section

The several amides and imides were obtained from commercial sources or synthesized by familiar methods and purified by recrystallization to melting points in good agreement with literature values.

In reaction mixtures for kinetic runs, the initial concentration of methyl iodide was typically *ca.* 0.02 *M*, of the sodium derivative of the amide or imide *ca.* 0.06 *M*, and of the free amide or imide variously from *ca.* 0.02 to 0.14 *M*. Details for particular runs are given in the Ph.D. thesis of Beale.[1] Second-order rate coefficients, k_2, were reckoned by linear regression analysis from the expression, $[1/(a - b)] \ln [b(a - x)/a(b - x)] = k_2 t$. In general, good second-order kinetics were observed. Enthalpies and entropies of activation were reckoned from standard expressions.[9]

(8) R. G. Bates, "Solute–Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969, p 52.

(9) J. F. Bunnett, "Investigation of Rates and Mechanisms of Reactions," S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., 2nd ed, Part I, Interscience, New York, N. Y., 1961, p 199.

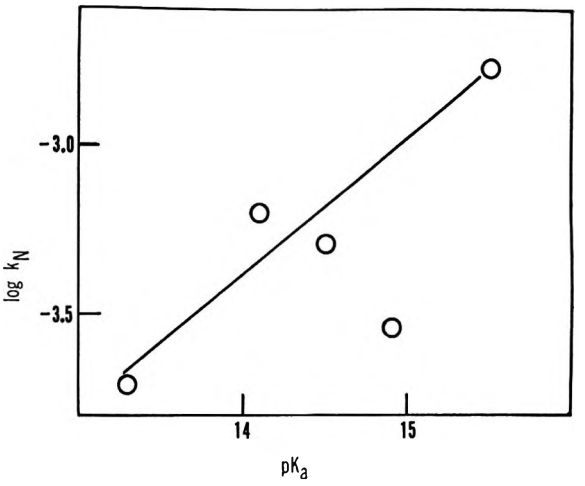


Figure 2.—Relationship of log k_N to pK_a in CH_3OH. From left to right, the points represent the anions of *N*-phenylbenzenesulfonamide, succinimide, phthalimide, benzenesulfonamide, and *N*-methylbenzenesulfonamide, respectively.

The expected *N*-methyl derivatives were isolated from reactions of succinimide, benzenesulfonamide, and *N*-methylbenzenesulfonamide under the conditions of rate measurement and were identified by melting point and/or infrared spectrum.

Registry No.—Methyl iodide, 74-88-4; $C_6H_5SO_2NCH_3^-$, 28627-66-9; succinimide anion, 28627-67-0; phthalimide anion, 28627-68-1; $C_6H_5SO_2NH^-$, 28627-69-2; $C_6H_5SO_2NC_6H_5^-$, 28627-70-5; $NaOCH_3$, 124-41-4.

Mercaptoethanol Catalysis for Hydrolysis of *N*-Benzyl-3-cyanopyridinium Bromide. A Model for the Nitrilase Reaction[1]

CONSTANTINE ZERVOS AND E. H. CORDES*[2]

Contribution No. 1928 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401

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The hydrolysis of *N*-benzyl-3-cyanopyridinium bromide is subject to marked catalysis by dilute aqueous solutions of mercaptoethanol. Under neutral or slightly acidic conditions, the predominant reaction product is the corresponding amide. Under conditions more acidic than pH 3, appreciable amounts of the corresponding acid are formed as well. First-order rate constants for the disappearance of nitrile at fixed concentrations of mercaptoethanol exhibit a bell-shaped dependence upon pH with a maximum near pH 7. First-order rate constants for the disappearance of nitrile at constant values of pH exhibit saturation with respect to mercaptoethanol concentration; under sufficiently basic conditions, excess mercaptoethanol actually causes inhibition of nitrile hydrolysis. These observations are interpreted in terms of (1) addition of mercaptoethanol to the nitrile function to form a thioimidate followed by hydrolysis of the thioimidate to yield the corresponding amide or acid, (2) addition of mercaptoethanol to both the nitrile and thioimidate to form 1,4 adducts which are kinetically inert, and (3) rate-determining formation of the thioimidate on the acidic side of the pH–rate maximum and rate-determining hydrolysis of this intermediate on the basic side.

Among functional groups at the acyl level of oxidation, nitriles are perhaps the most resistant to hydrolysis. The nitrile group is quite stable to both nucleophilic and electrophilic attack and, in consequence, strenuous conditions must usually be employed to effect hydrolysis under either basic or acidic conditions.[3-8] Nevertheless, enzymes have been identified in several sources which are capable of effecting rapid hydrolysis of nitriles at ambient temperatures in neutral aqueous solutions (see below). Our concern with these reactions centers on the elucidation of catalytic pathways through which these enzymes may function.

The basic hydrolysis of nitriles, including benzonitrile,[5,6] propionitrile,[7] and phenylacetonitriles,[9] is kinetically first order in both substrate and hydroxide

(1) Supported by Grant GE 3277 from the National Science Foundation and by Grant AM 08232 from the National Institutes of Health.

(2) Career Development Awardee of the National Institutes of Health, Grant K3 GM 10248-03; Research Fellow of the Alfred P. Sloan Foundation.

(3) J. D. McLean, B. S. Rabinovitch, and C. A. Winkler, *Can. J. Res., Sect. B*, **20**, 168 (1942).

(4) B. S. Rabinovitch, C. A. Winkler, and A. R. P. Stewart, *ibid.*, **20**, 121 (1942).

(5) K. B. Wiberg, *J. Amer. Chem. Soc.*, **77**, 2519 (1955).

(6) K. B. Wiberg, *ibid.*, **75**, 3961 (1953).

(7) B. S. Rabinovitch and C. A. Winkler, *Can. J. Res. Sect. B*, **20**, 185 (1942).

(8) R. Breslow, R. Fairweather, and J. Keana, *J. Amer. Chem. Soc.*, **89**, 2135 (1967).

(9) E. Angelescu, G. Vasiliu, and D. Zavoianu, *Rev. Chim., Acad. Repub. Pop. Roum.*, **7** (2), 655 (1962); *Chem. Abstr.*, **61**, 4168*d* (1962).

ion suggesting that the transition state involves the direct attack of hydroxide ion on the nitrile carbon atom; facile proton-transfer reactions complete amide formation. There appear to be two ways to promote amide formation from nitriles: increase in the electrophilicity of the nitrile carbon atom and utilization of nucleophilic reagents more reactive than hydroxide ion as nucleophilic catalysts.

That nitrile hydrolysis is subject to nucleophilic catalysis has been established by the observation that the addition of the hydroperoxide anion to nitriles is a facile reaction leading to the production of amide and molecular oxygen.[5,6] The kinetics of this reaction indicate that the rate-determining step is attack of the hydroperoxide anion on the nitrile followed by rapid decomposition of the resulting adduct to the indicated products. Since the hydroperoxide anion is less basic but more polarizable and more reactive toward nitriles than hydroxide ion, polarizability appears to be an important factor in determining nucleophilicity toward such substrates. This suggestion is supported by the observation that the weakly basic but highly polarizable hydrosulfide ion is also a good nucleophilic reagent against nitriles.[10,11]

The observation that nitriles are quite reactive toward sulfur nucleophiles is an interesting one biochemically since both ricinine nitrilase[12] and indolacetonitrile nitrilase[13] are subject to marked inhibition by reagents which bind thiol groups. Herein we present a detailed study of the catalysis of nitrile hydrolysis by mercaptoethanol. This system proves to have similarities with the enzymatic reactions involving similar substrates. A preliminary account of this work has been published.[14]

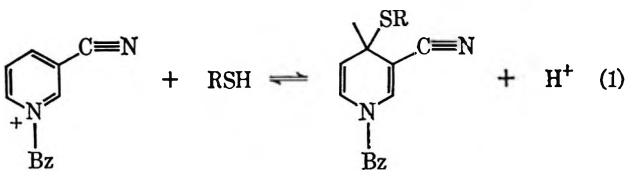
Experimental Section

Materials.—*N*-Benzyl-3-cyanopyridinium bromide was synthesized by refluxing a solution of 20 ml of α-bromotoluene and 20 g of 3-cyanopyridine in 150 ml of dry tetrahydrofuran for 20 min. The solution was cooled and concentrated under aspirator pressure and then under high vacuum until free of α-bromotoluene. The crystalline residue was recrystallized from *ca.* 500 ml of acetonitrile and dried under high vacuum, yield 35 g, mp 149°.[15]

Reagent grade mercaptoethanol (Matheson Coleman and Bell), ferric chloride (Fisher), hydroxylamine hydrochloride (Matheson Coleman and Bell), citric acid (Fisher), and tris(hydroxymethyl)aminomethane (Sigma) were used without further purification. Imidazole was recrystallized twice from benzene and freed of solvent by prolonged drying under high vacuum. All solutions were prepared in water which had been glass distilled with a Corning AG 1a still. Solutions of sodium hydroxide and hydrochloric acid were employed to adjust solutions to desired values of pH. CM Sephadex C 50 cation exchanger (Pharmacia Fine Chemicals) was prepared for use according to the instructions of the manufacturer.

Kinetic Methods.—The progress of kinetic runs was monitored by one of the following two methods.

A. At values of pH higher than 7, the concentrations of substrate and nucleophilic reagent ordinarily employed in the kinetic experiments, 4.4×10^{-3} *M* *N*-benzyl-3-cyanopyridinium bromide and up to 0.45 *M* mercaptoethanol, resulted in the formation of equilibrium concentrations of a 1,4 adduct sufficient to quantitate by its ultraviolet absorption at 332 mμ[16] (eq 1). Since (1) formation of this adduct is rapid with respect to the



rates of successive reactions (adduct formation is too fast to follow employing stopped-flow methods), (2) other intermediates and reaction products do not absorb appreciably at 332 mμ under the experimental conditions, and (3) the concentration of mercaptoethanol does not change appreciably during the course of the reaction, changes in the concentration of the substrate can be monitored by the optical density at this wavelength.[17]

B. At values of pH below 7 and within the range of concentrations normally employed for kinetic measurements (*vide infra*), insufficient 1,4 adduct is present at equilibrium in the reaction mixtures themselves to permit the reaction to be followed by observing its decay spectrophotometrically (eq 2). In these cases, changes in the concentration of substrate as a function of time were monitored by the periodic injection of 0.30-ml reaction solution aliquots into 2.7 ml of 0.1 *M* mercaptoethanol at pH 10.3 ± 0.2. The optical density of the adduct at 332 mμ was recorded as soon as possible.

Using either method, good first-order rate behavior is observed through at least three half-lives. First-order rate constants were, in all cases, obtained from the slopes of log $(OD_t - OD_\infty)$ against time plots employing a least-squares computer program and a CDC 3600/3400 computational facility. Derived rate and equilibrium constants were calculated from slopes and intercepts of double reciprocal plots of the observed rate constants against the concentrations of mercaptoethanol employing similar least-squares methods. Points obviously erratic were discarded. Reliable error estimates are not available.

Values of optical density were obtained employing a Zeiss PMQII spectrophotometer equipped with a cell holder through which water from a thermostated bath was continuously circulated. Temperature was maintained at 24.9° throughout. Ionic strength of reaction solutions was maintained at 0.60 through addition of NaCl. Values of pH were obtained with a Radiometer PHM 4c pH meter equipped with a glass electrode.

In some experiments, the concentration of a transient intermediate, the thio ester formed from mercaptoethanol and *N*-benzylnicotinic acid, was followed as a function of time by use of the neutral hydroxylamine–ferric chloride method as described by Jencks, *et al.*[18]

Product Analysis.—Determination of the products of decomposition of *N*-benzyl-3-cyanopyridinium bromide in aqueous solutions of mercaptoethanol was accomplished through two preparative runs.

In the first, 1.0 g of *N*-benzyl-3-cyanopyridinium bromide was dissolved in 20 ml of 0.5 *M* mercaptoethanol and permitted to remain at room temperature for 18 hr. The pH of the reaction mixture was 4.5 and did not change in the course of the reaction. At the end of the incubation period, the reaction solution was washed five times with equal volumes of ether and then concentrated to one-third the original volume under aspirator pressure. Crystallization of a product occurred during volume reduction. These crystals were collected, recrystallized from ethanol, and dried under high vacuum to yield 0.85 g, mp 235° (lit.[19] 236°). Ir, uv, and pmr spectra were identical with those of authentic *N*-benzyl-3-carbamoylpyridinium bromide. The product migrated with *N*-benzyl-3-carbamoylpyridinium bromide in ascending paper chromatography in an ethyl acetate–methanol–water

(10) K. Kindler, *Justus Liebigs Ann. Chem.*, **431**, 187 (1923).
(11) K. Kindler, *ibid.*, **450**, 1 (1926).
(12) W. G. Robinson and R. H. Hook, *J. Biol. Chem.*, **239**, 4257, 4263 (1964).
(13) K. V. Thimann and S. Mahadevan, *Arch. Biochem. Biophys.*, **105**, 133 (1964); **107**, 62 (1964).
(14) C. Zervos and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 6892 (1968).
(15) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *ibid.*, **88**, 3099 (1966).
(16) J. van Eys and N. O. Kaplan, *J. Biol. Chem.*, **228**, 305 (1957).
(17) Note that the mercaptoethanol adduct of the thioimidate intermediate (Scheme I) will absorb at the wavelength employed to follow the reaction kinetics. This could introduce an uncertainty into the assay method only if this adduct accumulated under conditions in which the formation of the thioimidate is rate determining. This is the rate-determining step under relatively acidic conditions as developed below; however, reasonable estimates for the equilibrium constant for adduct formation based on that for adduct formation from the substrate (Scheme I) indicate that, under the experimental conditions, this situation does not arise.
(18) W. P. Jencks, S. Cordes, and J. Carriuolo, *J. Biol. Chem.*, **235**, 3608 (1960).
(19) P. Karrer and F. J. Stare, *Helv. Chim. Acta*, **20**, 418 (1937).

(5:4:1) solvent system on Whatman No. 1 paper. *Anal.* Calcd for *N*-benzyl-3-carbamoylpyridinium bromide: C, 53.30; H, 4.44; N, 9.56. Found: C, 53.24; H, 4.55; N, 9.36.

In the second, 5.0 g of *N*-benzyl-3-cyanopyridinium bromide was dissolved on 200 ml of 0.5 *M* mercaptoethanol and 0.25 *M* citrate, pH 2.18. The reaction mixture was permitted to remain at room temperature for 22 days at which time the appropriate assays indicated that little substrate or thio ester remained. The reaction mixture was washed five times with equal volumes of ether and then subjected to chromatography on a column of CM Sephadex C50 which was 5 cm in diameter and 90 cm high. The column was eluted with 0.015 *M* phosphate buffer, pH 7.10 with which it had been preequilibrated. Fractions of 15 ml were collected employing a Gilson Model LB1 fraction collector equipped with volumetric collecting unit Model LVM1, and their optical density at 260 mμ was determined. Fractions containing the first peak were pooled and lyophilized. Following desalting by passage of an aqueous solution through a column of Sephadex G15, 100 mg of crystals was obtained. This was determined to be *N*-benzylnicotinic acid through identity of the ir and pmr spectra with those of an authentic sample of this compound. A second peak was treated as described above. These fractions yielded 120 mg of *N*-benzyl-3-carbamoylpyridinium bromide identified by paper chromatography and pmr spectroscopy. Attempts to purify the small amounts of the material eluting from the column between the two major fractions were not successful.

The above procedure was modified to determine the effects of pH on the nature of the reaction products. Four reactions were set up (see Table I). At the conclusion of the runs it was

TABLE I

	Reaction			
	A	B	C	D
pH	3.09	3.19	3.46	4.75
Citrate buffer, *M*	0.1	0.1	0.1	0.3
Mercaptoethanol, *M*	0.5	0.5	0.25	0.25
N-Benzyl-3-cyanopyridinium bromide, mg	250	250	200	200
Reaction volume, ml	10	10	40	40
Reaction time, hr	250	250	48	48

established by use of assay II that no substrate remained unreacted. In the cases of reactions A and B, the time course of disappearance of the substrate and the time course for appearance and disappearance of the thio ester intermediate were followed by the appropriate assays for about four half-lives. Each of the reaction mixtures was thoroughly washed with ether and then chromatographed on columns of CM Sephadex C 50, 2.5 cm in diameter and 45 cm high. As before these were developed with 0.015 *M* phosphate buffer, pH 7.1. The elution patterns were similar to that observed before, the acid appearing early in the process and the amide late with a small amount of unidentified material in between.

Ir spectroscopy was employed to follow the course of certain of the reactions of *N*-benzyl-3-cyanopyridinium bromide. The reaction solutions were prepared by dissolving 50 mg of *N*-benzyl-3-cyanopyridinium bromide in 1.0 ml of a 0.5 *M* solution of mercaptoethanol in deuterium oxide which had been adjusted to the desired value of pH with solutions of NaOD or DCl, as appropriate. The reaction solutions were then applied as a film to windows of IRTran-2 and assembled into cells. A Perkin-Elmer Model 621 infrared spectrometer was employed to record the spectra.

Results

Incubation of *N*-benzyl-3-cyanopyridinium bromide in aqueous solutions of mercaptoethanol in the pH range between 3 and 10 leads to a reasonably rapid disappearance of this material. As detailed in the Experimental Section, the predominant products of the reaction are the corresponding amide and acid, *N*-benzyl-3-carbamoylpyridinium bromide and *N*-benzylnicotinic acid. Under conditions more basic than pH 4, the amide is the only important product, while under more acidic conditions appreciable amounts of

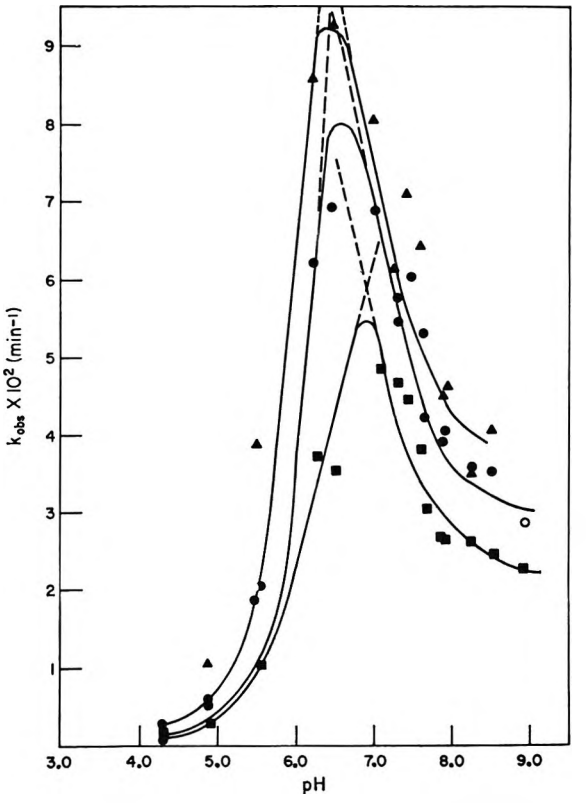


Figure 1.—First-order rate constants plotted against pH for the hydrolysis of *N*-benzyl-3-cyanopyridinium bromide in aqueous mercaptoethanol solutions. Experimental points (lines) refer to three mercaptoethanol concentrations, 0.04 *M* (closed squares), 0.08 *M* (closed circles), and 0.15 *M* (closed triangles).

the acid are formed as well. At pH 2.1, the acid is the more important product quantitatively.

In addition to the acid and amide, which are terminal products in the reaction process, evidence has been obtained to suggest that the thio ester between mercaptoethanol and *N*-benzylnicotinic acid is an intermediate. This suggestion is based on the observation of transient formation of a material which reacts with neutral hydroxylamine to yield a hydroxamic acid as judged from the nature of the color formed in the presence of acidic ferric chloride. This point is developed further below.

By employing either assay developed in the Experimental Section, the kinetics of disappearance of *N*-benzyl-3-cyanopyridinium bromide in aqueous solutions of mercaptoethanol at 25° were investigated. Pseudo-first-order rate behavior was observed throughout. In Figure 1, first-order rate constants for this reaction are exhibited as a function of the concentration of mercaptoethanol and pH.

In each case, the rate constants pass through a maximum as a function of pH. At low concentrations of mercaptoethanol, the maximum occurs near pH 7. As the thiol concentration is increased, the pH–rate maximum occurs at progressively more acidic values of pH, though not below pH 6 under any of the conditions examined in this study.

Saturation kinetics are observed with respect to mercaptoethanol concentration. That is, the apparent order of the reaction varies from unity to zero as the concentration of mercaptoethanol is increased. Such behavior is qualitatively accounted for in terms of

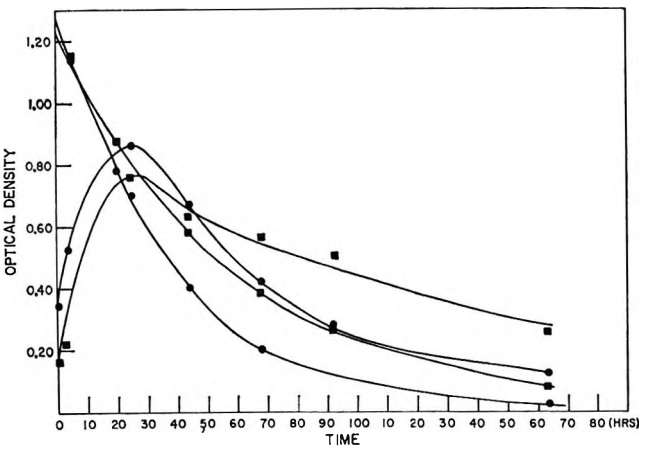


Figure 2.—Time course of disappearance (continuously declining curves) of the *N*-benzyl-3-cyanopyridinium ion and appearance of the neutral hydroxylamine–reactive intermediate (curves passing through a maximum), in aqueous mercaptoethanol solution at pH values below 3.5. Squares refer to reaction A and circles to reaction B (see Experimental Section).

the addition of mercaptoethanol to the substrate to form an unreactive complex (Experimental Section).

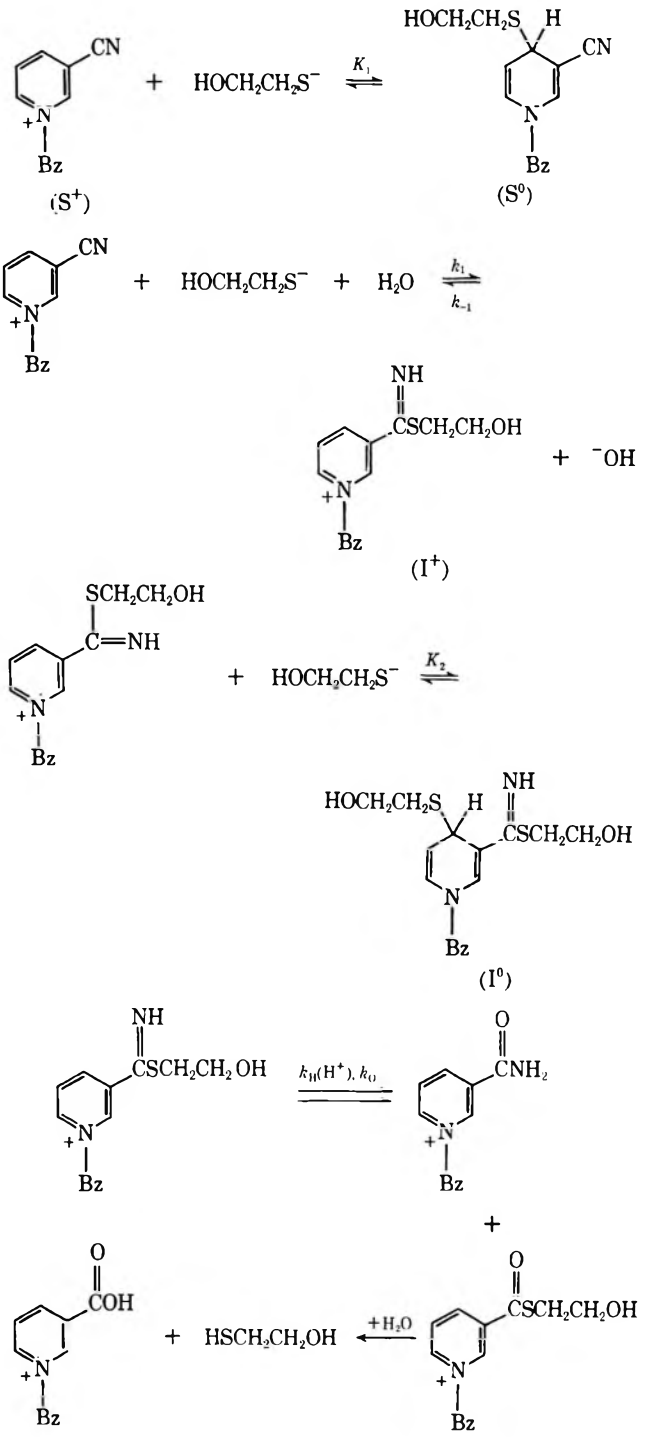
First-order rate constants for the disappearance of *N*-benzyl-3-cyanopyridinium bromide at pH 10.13 and ionic strength 0.20 decrease from 0.005 to 0.003 min^{-1} as the concentration of mercaptoethanol is increased from 0.02 to 0.20 *M*. This inhibition by thiol under basic conditions cannot be accounted for in terms of a single unreactive complex but requires, as is developed below, that a second unreactive complex be formed containing 2 molecules of thiol.

The time course of disappearance of *N*-benzyl-3-cyanopyridinium bromide and the time course of appearance and disappearance of a neutral hydroxylamine–reactive intermediate, presumably 2-hydroxyethyl-*N*-benzylthionicotinate, are shown in Figure 2. Reaction conditions for these kinetic studies have been described in the Experimental Section.

The time course of hydrolysis of *N*-benzyl-3-cyanopyridinium bromide to the corresponding amide on the alkaline side of the pH–rate maximum (Figure 1) was followed by ir spectroscopy as described in the Experimental Section. Under these conditions, one observes the immediate appearance of a new band at 1662 cm^{-1} which increases in intensity with time. In addition, one observes the immediate appearance of a new band at 1578 cm^{-1} the intensity of which decreases as a function of time. These observations contrast with those observed for the same reaction on the acid side of the pH–rate maximum. Here one finds only the gradual appearance of a new band at 1667 cm^{-1}, presumably due to the formation of the amide product.

In Figure 3, optical density values at 332 mμ are plotted against mercaptoethanol concentration for an aqueous solution of *N*-benzyl-3-cyanopyridinium bromide at pH 9.2, ionic strength 0.60, and 25.0°. The optical density values are assumed (*vide infra*) to be proportional to the concentration of the 1,4 adduct between *N*-benzyl-3-cyanopyridinium bromide and mercaptoethanol. They were obtained by extrapolating to "zero time" the semilogarithmic plots of a series of reactions run under these conditions. These conditions avoid the formation of large concentrations of the 1,4 adduct between the imidate intermediate and mercaptoethanol (Scheme I) for the reasons cited in the Discussion.

SCHEME I



Note that the midpoint of this curve, 0.006 *M* mercaptoethanol anion, is equal to the reciprocal of the sum of association constants for formation of the 1,4 adduct and thioimidate (Scheme I). Evaluation of these association constants independently is considered further in the Discussion.

Discussion

The results cited above indicate that mercaptoethanol is an effective catalyst for the hydrolysis of *N*-benzyl-3-cyanopyridinium bromide. There is no

simple way to express the magnitude of the catalysis since the uncatalyzed hydrolysis is simply first order in hydroxide ion under the conditions investigated here, while the catalyzed reaction exhibits a complex order with respect to mercaptoethanol and exhibits a pH–rate maximum as well. Kosower and Patton have measured a second-order rate constant of 0.28 M^{-1} sec^{-1} for the attack of hydroxide ion on the *N*-methyl-3-cyanopyridinium ion under comparable conditions with those employed in this study.[20] Comparing the corresponding first-order rate constant for that reaction at pH 7 with our observed maximal velocity at the same pH, a rate accentuation of about 10^3 is obtained. This value is about one order of magnitude smaller than one obtained in a similar study from this laboratory employing the *N*-benzyl substrate (unpublished observations).

The various characteristics of the mercaptoethanol-catalyzed hydrolysis of *N*-benzyl-3-cyanopyridinium bromide developed above suffice to indicate that the reaction is a complex one. The simplest reaction pathway that can account for the data is that shown in Scheme I. This reaction pathway includes (1) addition of thiol to the pyridinium ion at the 4 position to form an unreactive complex (S^0); (2) attack of the thiol, as the anion, on the cyano function of the substrate with formation of the corresponding thioimidate (I^+); (3) addition of the thiol to the thioimidate at the 4 position with formation of a second unreactive complex (I^0); and (4) hydrolysis of the thioimidate either to generate the amide directly or to generate the thio ester which may then hydrolyze to the acid.

The pathway indicated in Scheme I qualitatively accounts for the characteristics of the reaction in the following ways.

First, the saturation kinetics observed with respect to mercaptoethanol can be understood on the basis of the addition of the anion of mercaptoethanol to the substrate to form the 1,4 adduct which is unreactive toward attack by the thiol at the cyano function. That the complex should be much less reactive toward nucleophilic attack at the cyano group is entirely reasonable since (1) the activating electron-withdrawing effect of the cationic pyridinium nitrogen atom has been lost, and (2) electron donation by resonance from the ring nitrogen atom to the cyano function has been introduced. Overall, addition of the thiol to the ring system has transformed a strongly electron-withdrawing site into a strongly electron-donating one. A diminution of reactivity toward nucleophilic attack of 10^6 might well be expected to result. Furthermore, the formation of an adduct can be directly demonstrated spectrophotometrically and, in fact, serves as the basis for the rate measurements reported in this study. The observation of an absorption maximum for the adduct at 332 mμ is entirely consistent with the assignment of position 4 as the site of addition of the thiol although it does not rigorously exclude addition at sites 2 or 6. The assignment is further supported by observations that indicate that nucleophilic addition to 3-carbamoylpyridinium ions ordinarily is favored kinetically at the 4 position.[21] Since formation of the adduct at concentrations of mercaptoethanol employed in these kinetic studies is too fast to be measurable employing stopped-flow methods, it follows that adduct formation may be considered to be an equilibrium process, as indicated in Scheme I.

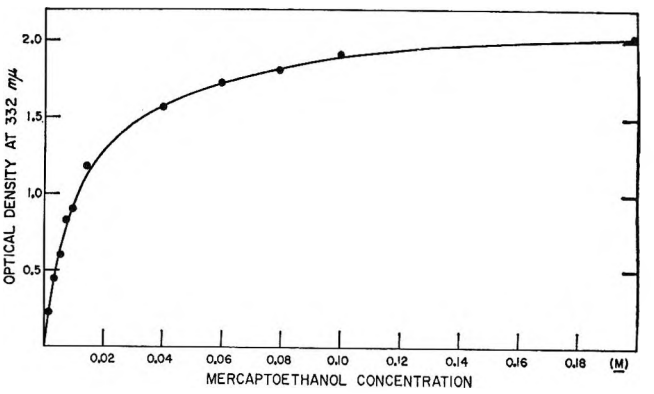


Figure 3.—Titration curve of *N*-benzyl-3-cyanopyridinium bromide with mercaptoethanol at pH 9.2, ionic strength 0.6, and 24.9°. The "zero time" optical density at 332 mμ (see text for details), which is proportional to the concentration of the 1,4 adduct between the substrate and mercaptoethanol anion, is plotted against the total mercaptoethanol concentration.

Second, the inhibition of the reaction by high concentrations of mercaptoethanol under relatively basic conditions (see Results) is accounted for in terms of the formation of an unreactive adduct between the thioimidate and a second molecule of mercaptoethanol. This intermediate, for which no direct spectrophotometric evidence is available, is expected to be unreactive toward nucleophilic attack by water compared to the corresponding pyridinium ion for the reasons developed just above. Assignment of the structure of the 4 adduct is arbitrary but reflects the kinetic reactivity of this position in relation to the 2 and 6 positions as previously pointed out. Accumulation of the thioimidate–mercaptoethanol adduct is expected to be important only under the conditions of high basicity since (1) the thioimidate is considered to accumulate only under these conditions (see below) and (2) adduct formation involves the thiolate ion, not the free thiol. Adduct formation is regarded as an equilibrium process in analogy with the behavior observed for adduct formation from the nitrile substrate.

Third, the pH–rate maximum observed for mercaptoethanol-catalyzed hydrolysis of *N*-benzyl-3-cyanopyridinium bromide (Figure 1) is interpreted as reflecting a transition from rate-determining formation of the thioimidate under acidic conditions to rate-determining hydrolysis of this intermediate under basic conditions. Such a transition in the rate-determining step is reasonable since formation of the adduct depends kinetically on the basic form of the nucleophilic reagent and, hence, the rate will increase with increasing pH below pH 9 and become pH independent above this value. In contrast, hydrolysis of the thioimidate very likely proceeds through acid-catalyzed and pH-independent reaction pathways reflecting, respectively, attack of water and hydroxide ion on the protonated substrates. These considerations are expressed diagrammatically in Figure 1. Related transitions in the rate-determining step have been observed for a number of reactions

(20) E. M. Kosower and J. W. Patton, *Tetrahedron*, **22**, 2081 (1966).

(21) R. N. Lindquist and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 1269 (1968).

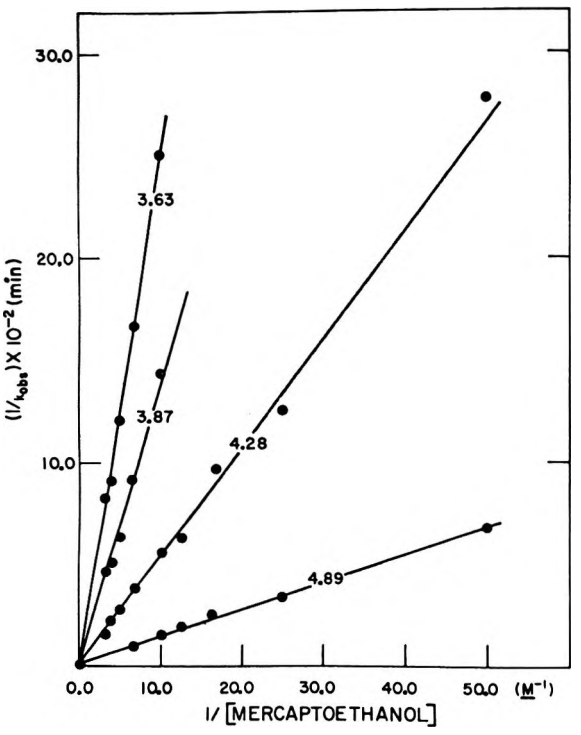


Figure 4.—Selected double reciprocal plots of k_{obsd} *vs.* mercaptoethanol concentration for the hydrolysis of *N*-benzyl-3-cyanopyridinium bromide in aqueous mercaptoethanol solutions on the acidic side of the pH–rate maximum, 25°, and ionic strength 0.60. The pH values of the reaction solutions are shown on the graph.

including carbonyl addition reactions,[22,23] Schiff base hydrolysis,[24] ester aminolysis,[25,26] thio ester hydrolysis,[27] and others.

Fourth, the course of the reaction as revealed by infrared spectroscopy is consistent with Scheme I (see Results). On the alkaline side of the pH–rate maximum, in which decomposition of the thioimidate is thought to be rate determining, the immediate appearance of the new band at 1662 cm^{-1} must reflect the rapid formation of equilibrium concentrations of the thioimidate. Increase in the intensity of this band reflects formation of the amide product whose infrared spectrum in this region is difficult to distinguish from that of the thioimidate. The new band at 1578 cm^{-1}, which appears immediately and decreases in intensity with time, is reasonably attributed to the thioimidate alone. On the acid side of the pH–rate maximum, in which formation of the thioimidate is considered to be rate determining, only the gradual appearance of a new band at 1666 cm^{-1} is observed, reflecting the gradual formation of the amide product.

Fifth, the pH dependence of the product distribution is accounted for in terms of the modes of partitioning of the thioimidate intermediate. Chaturvedi, MacMahon, and Schmir[25,28,29] have specifically investigated the decomposition of tetrahedral intermediates formed from the addition of water to thioimidates and have observed a transition from the expulsion of thiol with formation of amide to dominant expulsion of the amine with formation of the thio ester as the pH of the solution is lowered (Scheme II). Such behavior is completely consistent with that observed in our study and constitutes a strong line of evidence favoring the intermediate formation of the thioimidate.

Finally, the transient appearance of a material reactive toward neutral hydroxylamine suggests the presence of the thio ester intermediate (Figure 2). The kinetics of appearance and disappearance of this material is consistent with its participation as a reaction intermediate. Furthermore, under the conditions of these experiments, the maximum amount of thio ester formed is never more than 5% of the total amount of substrate utilized, consistent with the observation that the amide is the major reaction product.

Taken together, these lines of evidence provide a strong case for the reaction pathway of Scheme I. It is, of course, possible that the pathway is actually somewhat more complicated than this. Nevertheless, all of the features of Scheme I do seem to be required by the data which is accounted for within the limits of accuracy by it. We turn now to a consideration of the quantitative aspects of this reaction pathway and to the establishment of the rate and equilibrium constants which characterize it.

The complexity of the reaction pattern (Scheme I) precludes the derivation of a tractable rate law applicable to the total span of pH values for the kinetic experiments. No steady-state assumption valid over the whole pH range can be made for the concentration of the thioimidate involved in the reaction pathway. The derivation of two rate equations, one for each limb of the pH–rate profile, thus becomes necessary.

To the left of the pH–rate maximum, where the rate-determining step is the attack of the mercaptoethanol anion on the substrate, kinetically pertinent equations are depicted in the first two equations of Scheme I. The appropriate rate law is [$K_n \ll (H^+)$]

$$k_{obsd} = \frac{k_1(RSH)_T K_n}{(H^+) + K_1 K_n (RSH)_T} \quad (2a)$$

or

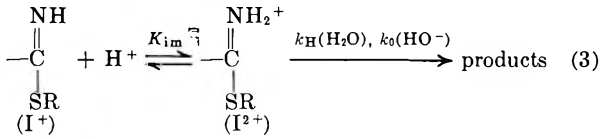
$$1/k_{obsd} = \frac{(H^+)}{k_1 K_n} \frac{1}{(RSH)_T} + \frac{K_1}{k_1} \quad (2b)$$

Equation 2b predicts that a double reciprocal plot of k_{obsd} *vs.* $(RSH)_T$ ought to be a straight line with the slope equal to $(H^+)/k_1K_n$ and the intercept equal to K_1/k_1. A series of such plots for several values of pH are collected in Figure 4. A secondary plot of slope against (H^+) (not shown) yields a straight line with the slope equal to $1/k_1K_n$. The value of K_n was obtained by independent titration under the reaction conditions of temperature and ionic strength and found identical within experimental error with the one appearing in the literature,[30] $K_n = 3.16 \times 10^{-10}$ *M*. This value of K_n and the secondary-plot slope suffice to determine k_1 ($k_1 = 1.5 \times 10^{-3}$ M^{-1} min^{-1}). This value of k_1 together with the intercepts of the primary plots (Figure 4) should suffice to establish K_1. These intercepts, however, are small and

(22) W. P. Jencks, *J. Amer. Chem. Soc.*, **81**, 475 (1959).
(23) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962).
(24) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).
(25) G. L. Schmir, *ibid.*, **90**, 3478 (1968).
(26) E. S. Hand and W. P. Jencks, *ibid.*, **84**, 3505 (1962).
(27) L. R. Fedor and T. C. Bruice, *ibid.*, **87**, 4138 (1965).
(28) R. K. Chaturvedi, A. E. McMahon, and G. L. Schmir, *ibid.*, **89**, 6984 (1967).
(29) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **91**, 737 (1969).
(30) J. T. Edsall and J. Wyman, "Biophysical Chemistry," Academic Press, New York, N. Y., 1958.

scatter widely precluding such calculation without large uncertainty. However, the reciprocal of the concentration of mercaptoethanol required to reach one-half of the maximal concentration of the adduct (Figure 3), 165 M^{-1}, is just the sum of the equilibrium constants for the adduct and thioimidate formation. Since that for the former is likely to be the greater of the two, this value may approximate K_1.

The rate law applicable to values of pH to the right of the pH–rate maximum may be derived on the basis of Scheme I assuming explicitly that hydrolysis of thioimidate is rate determining. Thioimidate hydrolysis occurs *via* attack of water and hydroxide ion on the protonated substrate.



(3)

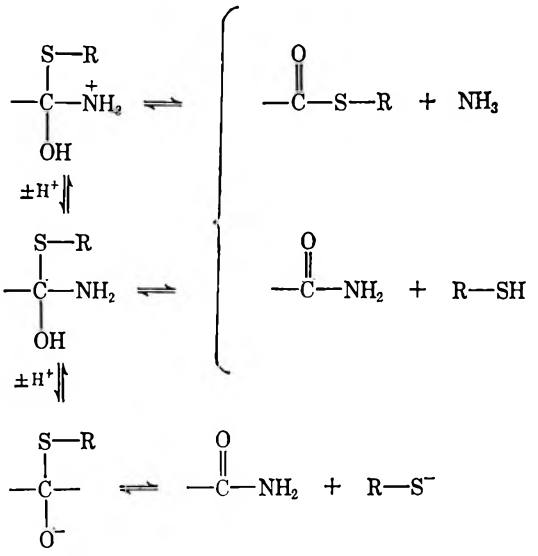
Letting $K_1' = k_1/k_{-1}$, and recognizing that $K_n < (H^+) < K_{im}$, one obtains

$$k_{obsd} = \frac{[k_H + k_0(OH^-)][(H^+)/K_{im}]}{1 + \frac{K_2K_n[RSH]_T}{(H^+)} + \frac{(OH^-)}{K_1'(RSH)_T} + \frac{K_w}{K_1'K_n(RSH)_T} + \frac{K_1(OH^-)}{K_1'}} \quad (4)$$

Although qualitative inspection of this rate law reveals that it is adequate to account for the experimental information, it is too complex to permit reliable derivation of values for individual rate constants.

There are three basic similarities between the catalysis of nitrile hydrolysis by mercaptoethanol described herein and that catalyzed by enzymes.[12,13] First, both the enzymatic and nonenzymatic processes result in marked catalysis; the enzymatic catalysis is, as usual, the more efficient of the two. Second, the enzymes, like mercaptoethanol, appear to be sulfhydryl reagents. Third, both the enzymatic and nonenzymatic reactions exhibit pH–rate maxima and the maxima occur at similar values of pH. It is true, however, that the pH–rate profiles are not identical in the various cases. This might reflect differences in the nature of thioimidates formed as reaction intermediates. If these similarities reflect more than coincidence, they suggest that the enzyme may function as a nucleophilic catalyst for nitrile hydrolysis in accord with the suggestion of Robinson, *et al.*[12] Moreover, the similarities suggest that an enzyme-bound thioimidate may be an intermediate and that decomposition of this intermediate is the rate-determining step on the alkaline side on the pH–rate maximum and, therefore, that this intermediate ought to be isolable and capable of characterization by the usual methods.

Scheme II



The central distinction between the enzymatic and nonenzymatic reactions is the observation that the former yield the acid almost exclusively as product[12,13] while the latter yields principally the amide except under quite acidic conditions. Schmir and his associates have demonstrated that the pathway for decomposition of imidates and thioimidates is subject to influence by bifunctional catalysts such as bicarbonate and the phosphate dianion.[25,28] Thus, were the nitrilases to employ a similar mode of catalysis for decomposition of the thioimidate intermediates, this difference would be accounted for in a natural manner.

Registry No.—*N*-Benzyl-3-cyanopyridinium bromide, 6516-53-6; mercaptoethanol, 75-08-1.

Kinetics and Mechanism for Pyruvic Acid Semicarbazone Formation[1]

TERESITA PINO AND E. H. CORDES*[2]

Escuela de Quimica, Facultad de Ciencias, Universidad Central, Caracas, Venezuela, and Department of Chemistry, Indiana University, Bloomington, Indiana 47401

Received September 3, 1970

Second-order rate constants or pyruvic acid semicarbazone formation exhibit a complex dependence on pH: in the pH ranges 0–2, 3–4, and 6–7, these constants are linearly dependent on the concentration of the hydrated proton; in the pH ranges 2–3 and 4–6, breaks in the pH-rate profile occur and the second-order rate constants are relatively insensitive to the concentration of the hydrated proton. These results suggest that, below pH 2, attack of semicarbazide on pyruvic acid is the rate-determining step, between pH 3 and 6, attack of semicarbazide on pyruvate is the rate-determining step, and, above pH 6, decomposition of the carbinolamine intermediate is rate determining. Second-order rate constants for pyruvic acid methyl ester semicarbazone formation exhibit only the latter break in the pH-rate profile in accordance with these suggestions. The attack of semicarbazide on pyruvate is subject to general acid catalysis by carboxylic acids; this catalysis is characterized by a value of the Brønsted exponent α of 0.37.

The kinetics of semicarbazone formation have been intensively studied in recent years.[3,4] It seems safe to conclude that the principal features of the mechanism for these reactions are in hand. Specifically, attack of semicarbazide, subject to marked specific and general acid catalysis, is the rate-determining step under mildly acidic conditions and dehydration of the carbinolamine intermediate, subject to marked specific acid catalysis and to weak general acid catalysis, is rate determining under neutral and basic conditions.[3] Nevertheless, these conclusions are based on studies employing a limited number of structurally related substrates. Consequently, expansion of kinetic investigation of semicarbazone formation to include substrates of novel structure is likely to provide further insight into the mechanism and catalysis for these reactions. Results of one such investigation, employing pyruvic acid and methyl pyruvate as substrates, is reported herein.

Experimental Section

Materials.—Pyruvic acid and methyl pyruvate were obtained commercially and were redistilled prior to use. Semicarbazide hydrochloride was recrystallized from ethanol–water several times prior to use. Solutions containing semicarbazide as the free base were prepared just prior to use. Other reagents employed were of reagent grade and were used without further purification. Glass distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a jacketed cell holder through which water from a constant temperature bath was constantly circulated.[4a,b] Temperature was maintained at 30° throughout. The extent of reaction was monitored by the increase in optical density near 240 mμ which accompanies semicarbazide formation. First-order rate constants, based on the total (hydrated + unhydrated) ketone, were obtained in the usual way from semilogarithmic plots of the difference in optical density at infinite time and at various times against time. Second-order rate constants under conditions in which semicarbazide attack is rate determining were calculated by dividing first-order rate constants by the concentration of semicarbazide free base. Second-order rate constants for semicarbazone formation in the region of rate-determining carbinolamine dehydration were calculated from the expression, $k_2 = k_1/(\text{semicarbazide})_{\text{free base}}$ (f) where f is the fraction of total substrate present as the (hydrated + unhydrated) ketone. Ionic strength was maintained at 0.50 throughout with KCl. Values of pH were obtained with a Radiometer Model 22 pH meter equipped with a glass electrode.

Equilibrium constant measurements for carbinolamine formation were made spectrophotometrically at 30° as previously described.[4a] A value of 3.65 for the pK_a of the conjugate acid of semicarbazide was employed.

Results and Discussion

For nonionizable substrates, the pathway for semicarbazone formation may be formulated as

$$\mathrm{RNH_2} + {>}\mathrm{C{=}O} \underset{k_{-2}(\mathrm{H^+})}{\overset{k_2(\mathrm{H^+})}{\rightleftharpoons}} \mathrm{RN(H)COH} \xrightarrow{k_3(\mathrm{H^+})} {>}\mathrm{C{=}NR} + \mathrm{H_2O} \qquad (1)$$

This pathway generates the following steady-state rate equation.[3]

$$v = \frac{k_3[k_1 + k_2(\mathrm{H^+})]}{[k_{-1}/(\mathrm{H^+}) + k_{-2} + k_3]}(\mathrm{RNH_2})({>}\mathrm{C{=}O}) \qquad (2)$$

Quite generally, under neutral or alkaline conditions the rate of dehydration of the carbinolamine is slower than that for its formation. Under these conditions, the rate law, in terms of first-order rate constants, becomes

$$k_{\text{obsd}} = k_3 k_{\text{eq}}(\mathrm{H^+})\frac{(\mathrm{RNH_2})}{1 + (\mathrm{RNH_2})K_{\text{eq}}} \qquad (3)$$

in which K_{eq} is the equilibrium constant for carbinolamine formation; $K_{\text{eq}} = k_1/k_{-1}$.

Jencks has previously shown that the reaction of pyruvate with semicarbazide at pH 6.5 obeys a rate equation of this form and, therefore, that dehydration of the carbinolamine must be rate determining at this pH.[4a] In Table I, values of first-order rate constants for this reaction in the region of rate-determining dehydration are collected for several concentrations of semicarbazide. These data clearly show, as expected on the basis of eq 3, that values of $k_{\text{obsd}}/(\mathrm{H^+})$ approach a limiting value as the concentration of semicarbazide is increased. This limiting value is just k_3 which has a value of $2.4 \times 10^6\ M^{-1}\ \text{min}^{-1}$. These data confirm the observation of Jencks noted above and provide a rate constant in reasonable agreement with a value of $4.8 \times 10^6\ M^{-1}\ \text{min}^{-1}$ measured at 25° and

(1) Supported by Grant AM 08232 from the National Institutes of Health and by the Escuela de Quimica, Universidad Central. Publication No. 1930 from the Department of Chemistry, Indiana University.

(2) Career Development Awardee of the National Institutes of Health; Research Fellow of the Alfred P. Sloan Foundation.

(3) Two comprehensive reviews are available: W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964); W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 10.

(4) Leading references include (a) W. P. Jencks, *J. Amer. Chem. Soc.*, **81**, 475 (1959); (b) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962); (c) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960); (d) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *ibid.*, **88**, 2225 (1966); (e) R. K. Chaturvedi and E. H. Cordes, *ibid.*, **89**, 4631 (1967).

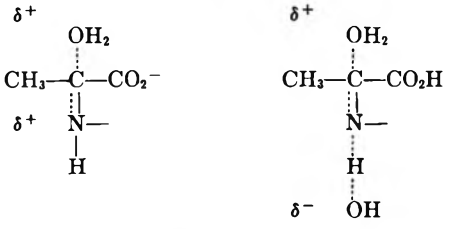
TABLE I

FIRST-ORDER RATE CONSTANTS FOR PYRUVATE SEMICARBAZONE FORMATION IN AQUEOUS SOLUTION AT 30° AND IONIC STRENGTH 0.50 UNDER CONDITIONS OF RATE-DETERMINING CARBINOLAMINE DEHYDRATION

Semicarbazide, M	pH	k_{obsd}, min^{-1}	$k_{obsd}/(H^+)$, M^{-1} min^{-1}
0.01	7.26	0.027	4.85×10^5
0.02	7.24	0.048	8.30×10^5
0.05	7.21	0.098	16.0×10^5
0.10	7.03	0.173	18.5×10^5
0.20	6.82	0.342	22.6×10^5
0.30	6.65	0.483	21.5×10^5

ionic strength 0.3 based on a single measurement at pH 6.5.[4a] Use of this value for k_3, the data of Table I, and eq 3 leads to a best value for K_{eq} near 30 M^{-1}. This value is somewhat larger than one of 10 M^{-1} measured at 25° and ionic strength 0.30. The latter value was measured spectrophotometrically rather than derived from kinetic data.[4a]

Note that there are several kinetically indistinguishable transition states for carbinolamine dehydration, two of which appear most reasonable: one based on addition of the amine to *pyruvate* coupled with specific acid catalysis of dehydration and one based on addition of amine to *pyruvic acid* coupled with both specific acid and base catalysis of dehydration.



In Figure 1, logarithms of second-order rate constants for pyruvate semicarbazone formation at 30° are plotted against pH over the pH range 0–8. Where necessary, these rate constants have been extrapolated to 0 buffer concentration. Above pH 7, for which carbinolamine dehydration is rate determining, these rate constants are, as developed above, first order in the concentration of the hydrated proton. The third-order rate constant, which is equal to $K_{eq}k_3$ (eq 1), is 7.2×10^7 M^{-2} min^{-1}.

Under slightly more acidic conditions, the second-order rate constants generate a break in the pH-rate profile diagnostic of a transition to rate-determining attack of semicarbazide on pyruvate.[3] Plots of the second-order rate constants in the pH range 3.5–5.5 against the concentration of the hydrated proton yield values of k_1 and k_2 (eq 1) of 80 M^{-1} min^{-1} and 2×10^6 M^{-2} min^{-1}, respectively.

The transition state for the acid-catalyzed reaction between pH 2 and 4 is again kinetically ambiguous; it may be regarded as acid-catalyzed attack of amine on pyruvate (as noted above) or as uncatalyzed attack of amine on pyruvic acid. These transition states differ only in the site of protonation of the pyruvate moiety. If the latter possibility is correct, the second-order rate constant for addition of semicarbazide to pyruvic acid, the product of the experimental third-order rate constant and the dissociation constant for pyruvic acid, is 6.3×10^3 M^{-1} min^{-1}. This value is considerably greater than the rate constant for

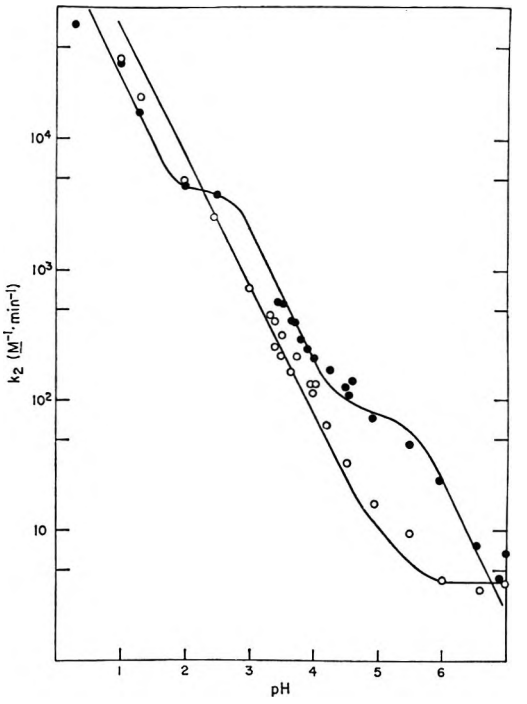


Figure 1.—Logarithm of second-order rate constants for semicarbazone formation from pyruvic acid (closed circles) and methyl pyruvate (open circles) measured at 30° and 0.50 ionic strength as a function of pH.

addition of semicarbazide to methyl pyruvate (see below). This result suggests that the former alternative is the correct one. However, the possibility of intramolecular general acid catalysis for the addition of semicarbazide to pyruvic acid, which may be important in the hydration of this substrate,[5,6] provides a possible explanation for this finding. Thus, although the data strongly suggest acid-catalyzed addition of semicarbazide to pyruvate, the alternative cannot be firmly excluded.

Under still more acidic conditions, a second break in the pH-rate profile is observed which occurs near the pK_a of pyruvic acid, 2.50.[7] This behavior reflects different reactivities of pyruvic acid and pyruvate anion toward nucleophilic attack by semicarbazide. The calculated third-order rate constant for acid-catalyzed attack of semicarbazide on pyruvic acid, k_2 of eq 1, is 3×10^5 M^{-2} min^{-1}. Thus pyruvate appears about sevenfold more reactive than pyruvic acid toward acid-catalyzed addition of semicarbazide. At first glance, this is a surprising conclusion since the carboxyl group of pyruvic acid is certainly more electron withdrawing than the carboxylate group of pyruvate. While this factor ought to increase the rate of attack of nucleophilic reagents at the carbonyl carbon, there are three other factors that need consideration as well. First, the effects of polar substituents on the rate of nucleophile attack and the extent of substrate protonation are opposite. Thus, the relatively electron-donating carboxylate group will favor substrate protonation compared to the carboxyl group. Second, aqueous solutions of pyruvic acid are converted more

(5) M. Eigen, K. Kustin, and H. Strehlow, *Z. Phys. Chem.* (*Frankfurt am Main*), **31**, 140 (1962).
(6) H. Strehlow, *Z. Electrochem.*, **66**, 392 (1962).
(7) W. P. Jencks and J. Regenstein, "Handbook of Biochemistry," H. A. Sober, Ed., The Chemical Rubber Co., Cleveland, Ohio, 1968, p J-150 ff.

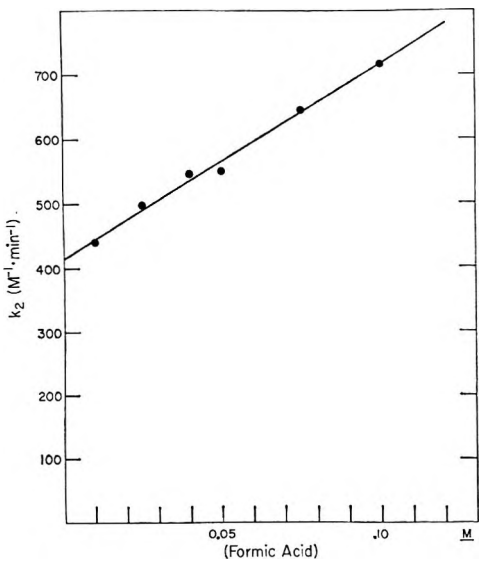


Figure 2.—Second-order rate constants for attack of semicarbazide on the pyruvate anion at 30° and pH 3.70 as a function of the concentration of formic acid.

fully to the unreactive hydrated form (*ca.* 65%) than are solutions of pyruvate (*ca.* 59%).[8,9] Finally, intramolecular general base catalysis by the pyruvate carboxylate group may contribute to its enhanced reactivity compared to pyruvic acid and methyl pyruvate (see below). The combination of these factors evidently outweighs the inherently greater electrophilicity of pyruvic acid compared to pyruvate. Of course, should the reaction from pH 2 to 4 reflect uncatalyzed attack of amine on pyruvic acid, these considerations become unnecessary.

These conclusions are strengthened by studies of the kinetics of pyruvic acid methyl ester semicarbazone formation. Second-order rate constants for this reaction are plotted against pH in Figure 1 for comparison with those for the corresponding reaction of pyruvate. Note that not all of the rate constants in the pH region greater than 3 have been extrapolated to 0 buffer concentration and may, therefore, be slighly too large. Nevertheless, the second-order rate constants and pH are best correlated by a single straight line with a slope of unity which breaks above pH 5 indicating a transition in rate-determining step. Note that the reactivity of pyruvate methyl ester toward attack by semicarbazide is nearly equal to that for pyruvic acid as expected on the basis of the similarity of the carboxyl and carbmethoxy groups. What is surprising is that the pyruvate anion appears to be about 20 times as reactive as pyruvate methyl ester toward water-catalyzed attack of semicarbazide (Figure 1). Differences in substrate hydration and basicity and intramolecular carboxylate catalysis may account for this difference.

The attack of semicarbazide on the pyruvate anion (or the kinetic equivalent) is subject to general acid catalysis by carboxylic acids. In Figure 2, second-order rate constants for this reaction at pH 3.70 are plotted as a function of the concentration of formic acid. Third-order rate constants evaluated from plots of this type for four carboxylic acids are collected in Table II. These values are well correlated by a single straight line in a Brønsted plot with a slope of 0.37. This value, while not large, is somewhat greater than those previously observed for general acid catalysis of semicarbazone formation.[4] This is a surprising finding since the pyruvate anion is the most reactive substrate for which general acid catalysis of semicarbazide attack has yet been studied and the transition state might have been expected to be reached progressively earlier along the reaction coordinate as the substrate becomes more reactive.[10-12] This suggests that values of Brønsted exponents should decrease with increasing substrate reactivity. It is, of course, possible that the degree of proton transfer in the transition state, as measured by the Brønsted exponent, is not representative of progress along the reaction coordinate. Finally, it is possible that the observed catalysis reflects general base catalysis of the attack of semicarbazide on pyruvic acid which, then, would have a value of $\beta = 0.63$.

TABLE II

CATALYTIC CONSTANTS FOR SEVERAL ACIDS FOR THE ATTACK OF SEMICARBAZIDE ON PYRUVATE AT 30°

Catalyst	pH	Concn range, *M*	pK_a	$k_3 \times 10^{-3}$, M^{-2} min^{-1}
Cyanoacetic acid	2.49	0.02–0.15	2.45	13.4
Chloroacetic acid	3.00	0.008–0.06	2.90	7.2
Formic acid	3.70	0.01–0.10	3.75	3.0
Acetic acid	4.00	0.015–0.24	4.76	1.4

Registry No.—Pyruvic acid semicarbazone, 2704-30-5.

(8) V. S. Griffiths and G. Socrates, *Trans. Faraday Soc.*, **63**, 673 (1967).
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Kinetic and Spectral Study of Some Reactions of 2,4,6-Trinitrotoluene in Basic Solution. I. Deprotonation and Janovsky Complex Formation[1]

Claude F. Bernasconi

University of California, Santa Cruz, California 95060

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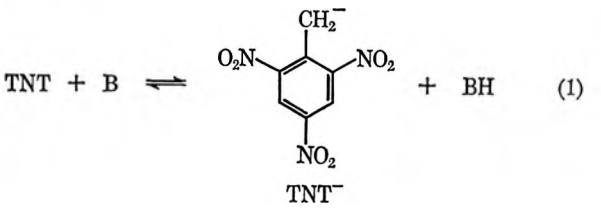
Three relatively fast kinetic processes can be detected in reactions of 2,4,6-trinitrotoluene (TNT) with lyate ions in methanol, ethanol, and in 50% dioxane–50% water. With the base in excess over TNT, formation of the 2,4,6-trinitrobenzyl anion (TNT^-) is the principal process. At high base concentration a second much faster process emerges, which is difficult to identify but could be due to a Meisenheimer complex (MC) coupled to a radical-anion formation. When TNT is in excess over the base, formation of a Janovsky complex (JC) between TNT^- and a second molecule of TNT is observed, which is identified through its visible spectrum. Rate constants of TNT^- and JC formation and reversion were measured. Preliminary spectral evidence indicates that in 10% dioxane–90% water TNT behaves differently from the other solvent systems.

The reaction of 2,4,6-trinitrotoluene (TNT) with strong bases has been interpreted as to produce the 2,4,6-trinitrobenzyl anion (TNT^-),[2,3] as shown in eq 1.



Extensive kinetic investigations of this reaction in ethanolic solutions have been reported[2] and some evidence supporting formation of TNT^-, including the observation of a large primary deuterium isotope effect,[2b] was advanced.[2]

Later, hydrogen exchange experiments in dimethylformamide–D_2O[3b] and in pyridine–D_2O[3c] provided more direct evidence in support of proton abstraction from the methyl group, though Bowden and Stewart[4] could not detect any appreciable hydrogen exchange in alkaline aqueous dimethyl sulfoxide. Furthermore Servis[5] argued against the possibility of TNT^- formation on the grounds of a comparison with the acidity of 2,4,6-trinitroaniline and "the generally known fact that amines are on the order of 10^{10} more acidic than corresponding hydrocarbons." Nevertheless, Crampton[6] states in a recent review that "present evidence suggests, on balance, that the violet color produced in alcoholic media is due to TNT^-, though adducts formed by the addition of alkoxide ion, or the TNT^- itself, to TNT may be produced in some circumstances."

Ainscough and Caldin[7] have indeed observed another interaction between TNT and the ethoxide ion in ethanol at high base concentrations. This interaction was attributed to a charge transfer (CT) complex, though the possibility of a Meisenheimer complex (MC)[8] was not excluded.

We expected that a thorough kinetic investigation of the interaction of TNT with OH^- in aqueous solution, with CH_3O^- in methanolic solution, and some further study with EtO^- in ethanolic solution would yield a better understanding of the chemistry of TNT. We wish now to report the first part of such a study.

Results

TNT and CH_3O^- in Methanol.—A temperature-jump[9] study of this system at wavelengths between 415 and 585 mμ revealed the presence of three well-separated relaxational processes, which we shall designate by τ_1, τ_2, and τ_3. Under the conditions used in this study, τ_1 is found to be in the time range of about 1 or 2 msec and τ_2 between 0.3 and 1 sec, whereas for τ_3 the time range is between 10 and 30 msec.

The two slower relaxation times (τ_2 and τ_3) were easily measurable; representative oscilloscope traces are displayed in Figure 1b and c. τ_1 on the other hand, was barely detectable with the technique available; Figure 1a shows an oscilloscope trace, where this latter process can be recognized as a little hump on top of the other curve (τ_3). No study of the concentration dependence of τ_1 could be carried out and only a very crude estimate of the relaxation time could be made from this or similar pictures; τ_1 is believed to be somewhere between 0.4 and 2.0 msec.

τ_2 and τ_3 as determined at various concentrations of TNT and $NaOCH_3$ in CH_3OH are reported in Table I; the electrolyte concentration was kept constant at 0.5 *M* in all runs by addition of appropriate amounts of $NaClO_4$. The slowest process, τ_2, can be observed over a wide concentration range of $NaOCH_3$ and TNT; most measurements of τ_2 were made with $NaOCH_3$ in large excess over TNT, though two experiments were performed with TNT in large excess over $NaOCH_3$ and three experiments where the concentrations of both reactants were low and the same or of the same order of magnitude.

Two observations are noteworthy. (1) The relative amplitudes (fractional change of optical density immediately following a temperature jump, $\Delta OD/OD$) are appreciably greater when the base concentration exceeds the TNT concentration compared to the converse situation. (2) When τ_2^{-1} is plotted *vs.* the sum of [TNT] + [NaOMe], one recognizes two sets of points: τ_2^{-1} values determined from experiments where

(1) Supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the donors of this fund.

(2) (a) E. F. Caldin and G. Long, *Proc. Roy. Soc. Ser. A*, **226**, 263 (1955); (b) J. A. Blake, M. J. B. Evans, and K. E. Russell, *Can. J. Chem.*, **44**, 119 (1966).

(3) (a) K. G. Shipp and L. A. Kaplan, *J. Org. Chem.*, **31**, 857 (1966); (b) E. Buncel, K. E. Russell, and J. Wood, *Chem. Commun.*, 252 (1968); (c) R. E. Miller and W. F. K. Wynne-Jones, *J. Chem. Soc.*, 2375 (1959).

(4) K. Bowden and R. Stewart, *Tetrahedron*, **21**, 261 (1965).

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(6) M. R. Crampton, *Adran. Phys. Org. Chem.*, **7**, 211 (1969).

(7) J. B. Ainscough and E. F. Caldin, *J. Chem. Soc.*, 2546 (1956).

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(9) M. Eigen and L. DeMaeyer in "Technique of Organic Chemistry," Vol. VIII, part 2, Interscience, New York, N. Y., 1963, p 895.

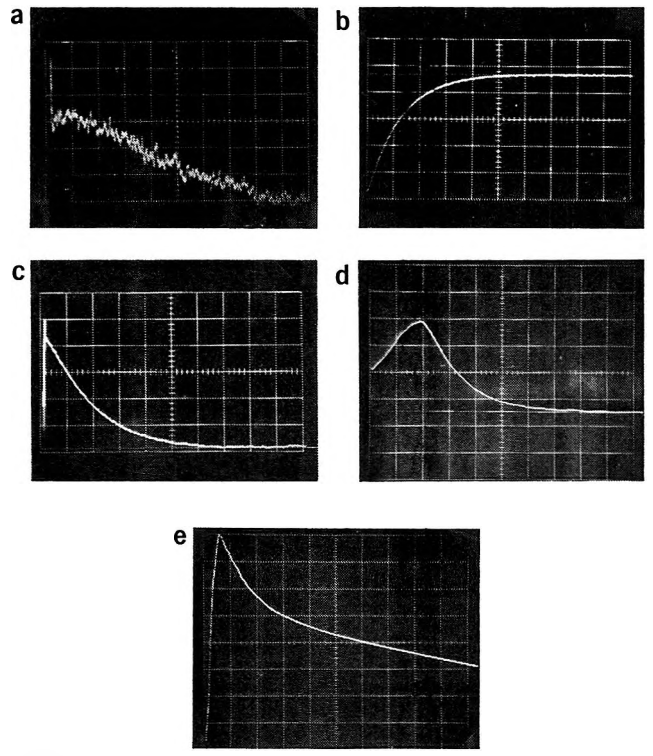


Figure 1.—Representative oscilloscope traces (ordinate in arbitrary units): (a) τ_1 in methanol, $[NaOMe]_0 = [TNT]_0 = 0.005\ M$, 450 mμ, 2 msec/horizontal division, temperature-jump method; (b) τ_2 in methanol, $[NaOMe]_0 = 0.05\ M$, $[TNT]_0 = 4 \times 10^{-4}\ M$, 500 mμ, 0.5 sec/horizontal division, temperature-jump method; (c) τ_3 in methanol, $[NaOMe]_0 = 0.001\ M$, $[TNT]_0 = 0.06\ M$, 425 mμ, 10 msec/horizontal division, temperature-jump method; (d) τ_1 in ethanol, $[NaOEt]_0 = 0.15\ M$, $[TNT]_0 = 5 \times 10^{-5}\ M$, 438 mμ, 5 msec/horizontal division, stopped-flow method; (e) τ_1 in 50% dioxane–50% water, $[NaOH]_0 = 0.2\ M$, $[TNT]_0 = 10^{-4}\ M$, 460 mμ, 100 msec/horizontal division, stopped-flow method.

TABLE I

INTERACTION OF TNT WITH MeO^- IN METHANOL

$[NaOCH_3]_0$, M	$[TNT]_0$, M	$[NaClO_4]$, M	τ_2^{-1}, sec^{-1}	τ_3^{-1}, sec^{-1}
≈0.0005	0.0005	0.5	0.94 ± 0.15	
0.002	0.002	0.5	1.08 ± 0.05	
0.008	0.002	0.49	1.24 ± 0.06	
0.05	0.0004	0.45	1.74 ± 0.10	
0.10	10^{-4}	0.40	2.34 ± 0.13	
0.15	10^{-4}	0.35	2.93 ± 0.20	
0.20	10^{-4}	0.30	3.92 ± 0.30	
≈0.0002	0.01	0.50		29.3 ± 1.5
≈0.001	0.01	0.50		30.5 ± 1.5
≈0.001	0.02	0.50		32.2 ± 1.5
≈0.001	0.04	0.50		39.3 ± 1.8
≈0.001	0.06	0.50	1.26 ± 0.07 (1.30)	51.4 ± 2.6
≈0.0005	0.08	0.50		59.8 ± 3.0
≈0.0005	0.10	0.50	1.66 ± 0.12 (1.71)	65.4 ± 3.2
≈0.0005	0.12	0.05		75.1 ± 3.5

either [NaOMe] ≫ [TNT] or where both reagents were at very low concentrations lie on a straight line, whereas τ_2^{-1} values from experiments where [TNT] ≫ [NaOMe] are definitely below that line (Figure 2).

These apparent anomalies are resolved when τ_3 is considered. τ_3^{-1} values could easily be measured only when TNT was chosen as the excess component; in fact, τ_3 was then the predominant process. On the other hand, when the base is in excess, τ_3 is hardly detectable at all and only observed when the TNT concentration is fairly high. Moreover, in a series of temperature-jump experiments, the relative amplitudes (ΔOD/OD) of τ_3 remain about the same when the TNT concentration is increased, or even increased slightly, instead of decreasing steadily as is normally the case for a straightforward bimolecular reaction in which the relaxational behavior is monitored at some wavelength of product absorption.

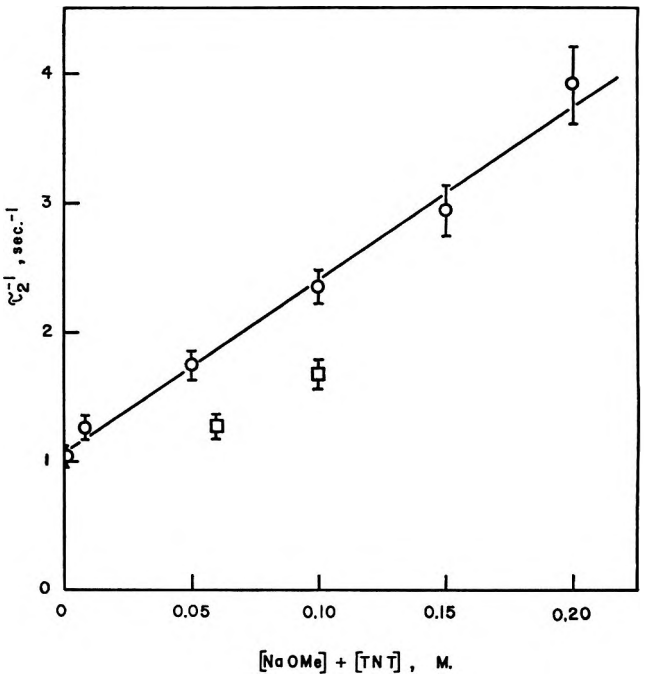


Figure 2.—Reaction of TNT with NaOMe in methanol; τ_2^{-1} as function of [NaOMe] + [TNT], □ for [TNT] ≫ [NaOMe], O for all the others.

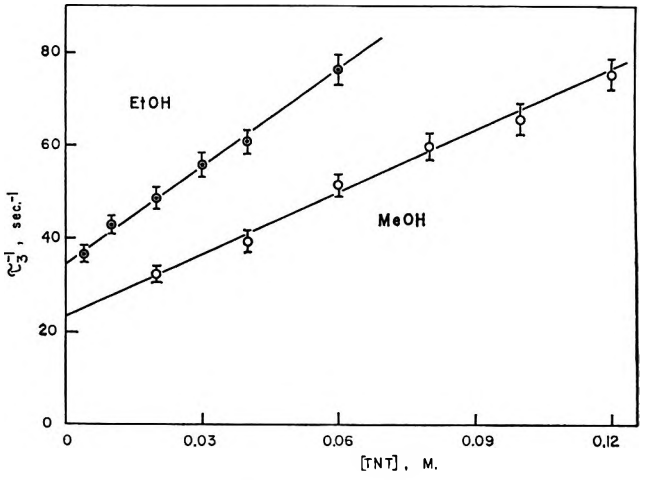


Figure 3.—Reaction of TNT with TNT^-; τ_3^{-1} as function of [TNT], O in methanol, ⊙ in ethanol.

When τ_3^{-1} is plotted *vs.* TNT concentration, a straight line results (Figure 3).

The foregoing experimental observations, as well as some spectral data discussed below, are consistent with Scheme I, R being CH_3. According to this scheme, τ_2 would arise from deprotonation of TNT to form the 2,4,6-trinitrobenzyl anion TNT^- and τ_3 from the reaction of TNT^- with a second molecule

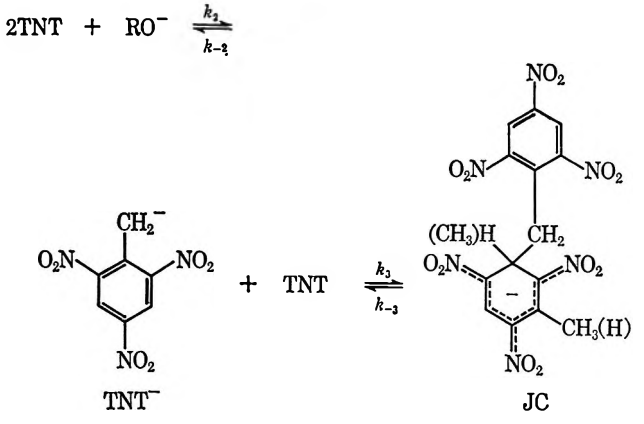
Table II

Rate and Equilibrium Constants for Deprotonation and Janovsky Complex Formation of TNT in Basic Methanol, Ethanol, and 50% Dioxane–50% Water at 25°

		Methanol	Ethanol	50% dioxane–50% water
TNT + RO⁻	k_2 (M^{-1} sec^{-1})	13.3 ± 0.6	82 ± 4 (62.5[a])	2.42 ± 0.12
$k_2 \downarrow\uparrow k_{-2}$	k_{-2} (sec^{-1})	1.07 ± 0.1	4.5 ± 0.5 × 10^{-2}	7.5 ± 1.0 × 10^{-3}
TNT⁻	$K_2 = \frac{k_2}{k_{-2}}$ (M^{-1})	12.4 ± 1.7 (7.1)[b]	1820 ± 270 (2040)[c]	323 ± 50
TNT + TNT⁻	k_3 (M^{-1} sec^{-1})	442 ± 20	700 ± 35	3400 ± 120
$k_3 \downarrow\uparrow k_{-3}$	k_{-3} (sec^{-1})	3.5 ± 1.5	34.5 ± 2.5	30 ± 3
JC	$K_3 = \frac{k_3}{k_{-3}}$ (M^{-1})	18.9 ± 2.0	20.3 ± 2.2	113 ± 15

[a] Reference 2a, at 19.1°. [b] Reference 22. [c] Reference 2a, at 25°.

Scheme I



of TNT to form the Janovsky[10,11] complex (JC). It is to be noted that the position of nucleophilic attack on TNT is unspecified. The origin of the barely detectable fast relaxation time, τ_1, can not be inferred from our experiments however.

Let us examine how the kinetic data do indeed fit with the proposed reaction scheme. The analytical expressions for τ_2 and τ_3 are relatively simple because $\tau_2 \gg \tau_3$ throughout. They are set forth in eq 2

$$\frac{1}{\tau_2} = k_2\left([\mathrm{TNT}] + [\mathrm{RO}^-]\frac{1 + 2K_3[\mathrm{TNT}]}{1 + K_3([\mathrm{TNT}] + [\mathrm{TNT}^-])}\right) + k_{-2}\frac{1 + 2K_3[\mathrm{TNT}^-]}{1 + K_3([\mathrm{TNT}] + [\mathrm{TNT}^-])} \quad (2)$$

and 3,[13] where all concentrations refer to their equilibrium values; K_3 is defined as k_3/k_{-3}.

$$\frac{1}{\tau_3} = k_3([\mathrm{TNT}] + [\mathrm{TNT}^-]) + k_{-3} \quad (3)$$

In principle, at least one of the terms in eq 2 or 3 should contain a correction factor taking into account the fast equilibrium process giving rise to τ_1. The very small amplitude of τ_1 suggests, that, whatever this process is, the equilibrium must strongly favor the reactants under the present reaction conditions so that this correction factor is equal to 1 for all practical purposes; as seen below, this is borne out by the strict adherence of the experimental data to eq 2 and 3.

In the experiments conducted for the determination of τ_3, $[\mathrm{TNT}]_0 \gg [\mathrm{NaOMe}]_0$ throughout, so that eq 3 is reduced to eq 4, where [TNT] is now equivalent

$$\frac{1}{\tau_3} = k_3[\mathrm{TNT}] + k_{-3} \quad (4)$$

to the stoichiometric concentration. Thus from the slope and intercept of the straight line in Figure 3, k_3 and k_{-3} were calculated; they are reported in Table II.

The experiments pertaining to τ_2 fall into two categories.

(1) The concentration of TNT is low with either $[\mathrm{NaOMe}]_0 \gg [\mathrm{TNT}]_0$ or $[\mathrm{NaOMe}]_0 \approx [\mathrm{TNT}]_0$. In either situation $K_3[\mathrm{TNT}] \ll 1$ and $K_3([\mathrm{TNT}] + [\mathrm{TNT}^-]) \ll 1$ and eq 2 becomes eq 5, where the

$$\frac{1}{\tau_2} = k_2([\mathrm{RO}^-] + [\mathrm{TNT}]) + k_{-2} \quad (5)$$

equilibrium concentrations can be replaced by the stoichiometric concentrations. A plot of τ_2^{-1} *vs.* ([NaOMe] + [TNT]) is indeed linear as shown in Figure 2; k_2 and k_{-2} were determined from the slope and intercept and are set forth in Table II.

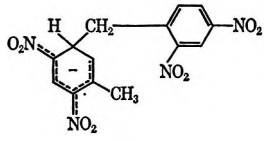
(2) The second category of experiments are those where $[\mathrm{TNT}]_0 \gg [\mathrm{NaOMe}]_0$, so that eq 2 becomes eq 6. For two experiments with the same concentration of the excess component, the excess component being NaOMe in the first, TNT in the second case, eq 6 predicts τ_2^{-1} to be lower by an amount equivalent to $k_{-2}K_3[\mathrm{TNT}]/(1 + K_3[\mathrm{TNT}])$ in the second case. The numbers in parentheses in Table I for the experiments at 0.06 and 0.1 *M* TNT refer to such relaxation times calculated from k_2, k_{-2}, and K_3 with reference to eq 6. As can be seen, the agreement between these and the experimental values is well within the experimental error.

$$\frac{1}{\tau_2} = k_2[\mathrm{TNT}] + k_{-2}\frac{1}{1 + K_3[\mathrm{TNT}]} \quad (6)$$

The observation of large relative amplitudes with τ_2 when [NaOMe] ≫ [TNT] but small ones when [TNT] ≫ [NaOMe], as well as the fact that the amplitudes of τ_3 increase slightly and then approximately level off when the TNT concentration is in-

(10) (a) J. V. Janovsky and L. Erb, *Ber.*, **19**, 2155 (1886); (b) R. J. Pollitt and B. C. Saunders, *J. Chem. Soc.*, 4615 (1965).

(11) Foster and Mackie[12] have previously suggested that a Janovsky complex is formed from 2,4-dinitrotoluene and ethoxide ion in ethanol.



(12) R. Foster and R. K. Mackie, *Tetrahedron*, **19**, 691 (1963).

(13) For general methods of derivation of equations like 2, 3, and others to follow below, see ref 9.

TABLE III
INTERACTION OF TNT WITH EtO^- IN ETHANOL

[NaOEt]$_0$, M	[TNT]$_0$, M	[$NaClO_4$], M	τ_1^{-1}, sec^{-1}	τ_2^{-1}, sec^{-1}	τ_3^{-1}, sec^{-1}
$\approx 2.5 \times 10^{-4}$	5×10^{-5}	0.40		0.057 ± 0.002	
$\approx 5 \times 10^{-4}$	5×10^{-5}	0.40		0.089 ± 0.003	
0.001	5×10^{-5}	0.40		0.121 ± 0.005	
0.002	5×10^{-5}	0.40		0.218 ± 0.01	
0.005	5×10^{-5}	0.395		0.45 ± 0.02	
0.01	5×10^{-5}	0.39		0.97 ± 0.03	
0.02	5×10^{-5}	0.38		1.90 ± 0.07	
0.03	5×10^{-5}	0.37		2.54 ± 0.10	
0.05	5×10^{-5}	0.35		3.99 ± 0.20	
0.075	5×10^{-5}	0.325		5.94 ± 0.24	
0.10	5×10^{-5}	0.30	179 ± 50	7.53 ± 0.30	
0.15	5×10^{-5}	0.25	209 ± 30	10.0 ± 0.40	
0.20	5×10^{-5}	0.20	235 ± 20	12.6 ± 0.60	
0.20	5×10^{-6}	0.20	165 ± 15		
0.20	2.5×10^{-5}	0.20	204 ± 20		
0.20	10^{-4}	0.20	283 ± 30		
0.20	2×10^{-4}	0.20	355 ± 35[a]		
$\approx 4 \times 10^{-4}$	0.004	0.20			36.6 ± 1.5
$\approx 10^{-4}$	0.01	0.20			42.0 ± 2.0
$\approx 2 \times 10^{-4}$	0.01	0.20			42.9 ± 2.0
$\approx 6 \times 10^{-4}$	0.01	0.20			40.6 ± 2.0
$\approx 2 \times 10^{-4}$	0.02	0.20			48.5 ± 2.2
$\approx 2 \times 10^{-4}$	0.03	0.20			55.7 ± 2.5
$\approx 2 \times 10^{-4}$	0.04	0.20			60.7 ± 2.5
$\approx 2 \times 10^{-4}$	0.06	0.20			76.2 ± 3.0

[a] The value of τ_1 does not change when 10^{-2} M or 5×10^{-2} M of 2-methyl-2-nitrosopropane is added.

creased, are equally consistent with the proposed scheme as will be shown now.[14]

The amplitude for τ_2, under the condition [NaOMe] ≫ [TNT], is given by eq 7, whereas for [TNT] ≫

$$\frac{\Delta OD}{OD} = \frac{\Delta K_2}{K_2(1 + K_2[RO^-])} \quad (7)$$

[NaOMe] it is given by eq 8; ΔOD is the change in

$$\frac{\Delta OD}{OD} = \frac{\Delta K_2}{K_2(1 + K_2[TNT] + K_2K_3[TNT]^2)} + \frac{\Delta K_3[TNT]}{(1 + K_3[TNT])(1 + K_2[TNT] + K_2K_3[TNT]^2)} \quad (8)$$

optical density; ΔK_2 and ΔK_3 are the changes in equilibrium constants K_2 and K_3 brought about by the temperature jump. These equations are derived in the Appendix; they are valid at those wavelengths chosen for monitoring the reaction, where only TNT^- and JC contribute significantly to the light absorption.

Let us compare two experiments, where the excess component in the first is NaOMe, in the second TNT, and its concentration is 0.1 M in either case. With K_2 and K_3 from Table II, one calculates ΔOD/OD = 0.036 ΔK_2 from eq 7 and ΔOD/OD = 0.0176 ΔK_2 + 0.0076 ΔK_3 from eq 8. ΔOD/OD in the latter experiment must indeed be much smaller[14] than in the former for two reasons. (1) The ΔK_2 factor is smaller. (2) ΔK_3 has a different sign from ΔK_2 as is apparent from Figure 1b and c. Thus the experimental observation of larger amplitudes where [NaOMe] ≫ [TNT] but small amplitudes when [TNT] ≫ [NaOMe] is consistent with Scheme I.

The amplitude of τ_3, for which all experiments were conducted with [TNT] ≫ [NaOMe], is given by eq 9, which is also derived in the Appendix. Equation 9

$$\frac{\Delta OD}{OD} = \frac{\Delta K_3[TNT](\epsilon_{JC} - \epsilon_{TNT^-})}{(1 + K_3[TNT])(\epsilon_{TNT^-} + \epsilon_{JC}K_3[TNT])} \quad (9)$$

shows that the amplitude and its concentration dependence should be a function of the wavelength. At a wavelength where the relation of the extinction coefficients is $\epsilon_{TNT^-} \gg \epsilon_{JC}$, |ΔOD/OD| increases with increasing TNT concentration until it reaches a plateau of |ΔOD/OD| = $\Delta K_3/K_3$ when $K_3[TNT] \gg 1$. On the other hand, when $\epsilon_{JC} \gg \epsilon_{TNT^-}$, |ΔOD/OD| will decrease indefinitely with increasing TNT concentration. Our experiments that were performed at 425 mμ, where ϵ_{TNT^-} = 4400 and ϵ_{JC} = 5600, lie somewhere between these extremes. (Determination of the extinction coefficients is discussed below.) Thus eq 9 becomes eq 10. By inserting K_3 from Table II, one

$$\frac{\Delta OD}{OD} = \frac{\Delta K_3[TNT]}{(1 + K_3[TNT](3.67 + 4.67\,K_3[TNT])} \quad (10)$$

can calculate the amplitude; it increased slightly from ΔOD/OD = 2.68×10^{-3} ΔK_3 at 0.02 M TNT to 3.16×10^{-3} ΔK_3 at 0.04 M TNT; at 0.06 M TNT it is 3.14×10^{-3} ΔK_3, at 0.08 M TNT it is 2.99×10^{-3} ΔK_3, and at 0.12 M TNT it is 2.58×10^{-3} ΔK_3. This is entirely consistent with experimental observation.

TNT and EtO^- in Ethanol.—This system has been studied before under conditions where [NaOEt] ≫ [TNT].[2a,7] The rate coefficient (k_2) for TNT deprotonation and the equilibrium constant (K_2) for this process,[2a] as well as an approximate rate coefficient (k_1) for a fast reaction attributed to a CT-complex formation,[7] were reported. The aims of the present study was to find evidence for the Janovsky complex, to measure directly the rate of reprotonation of TNT^-

(14) In these comparisons only the absolute values of ΔOD/OD are considered.

TABLE IV

INTERACTION OF TNT WITH OH^- IN 50% DIOXANE–50% WATER

$[NaOH]_0$, M	$[TNT]_0$, M	[NaCl], M	τ_1^{-1}, sec^{-1}	$10^3 \times \tau_2^{-1}$, sec^{-1}	τ_3^{-1}, sec^{-1}
0.001	5×10^{-5}	0.2		8.2 ± 2.0	
0.001	2×10^{-4}	0.2		8.5 ± 2.0	
0.002	2×10^{-4}	0.2		10.7 ± 2.0	
0.005	5×10^{-5}	0.195		18.1 ± 2.0	
0.025	2×10^{-5}	0.175		71.5 ± 4.0	
0.05	2×10^{-5}	0.15		132 ± 6.5	
0.075	2×10^{-5}	0.125		196 ± 10	
0.10	2×10^{-5}	0.10		238 ± 15	
0.10	10^{-4}	0.10	8.2 ± 3.0		
0.20	10^{-4}		9.2 ± 2.0		
0.20	2×10^{-5}		9.4 ± 2.0		
$\approx 4 \times 10^{-4}$	0.002	0.20			33.8 ± 4.0
$\approx 4 \times 10^{-4}$	0.005	0.20			48.2 ± 1.5
$\approx 2 \times 10^{-4}$	0.01	0.20			64.5 ± 2.5
$\approx 2 \times 10^{-4}$	0.015	0.20			77.7 ± 2.8
$\approx 2 \times 10^{-4}$	0.02	0.20			97.2 ± 3.0

(k_{-2}), and to get some preliminary idea on the nature of the fast process reported by Ainscough and Caldin.

Experiments in the stopped-flow and temperature-jump apparatus showed indeed the presence of three relaxation times, with a similar pattern as in methanol; *i.e.*, τ_1 is the fastest, τ_2 the slowest, and τ_3 intermediate and only present at relatively high TNT concentrations. τ_2 and τ_3 are attributed to the processes of Scheme I, just as for methanol. The results are summarized in Table III.

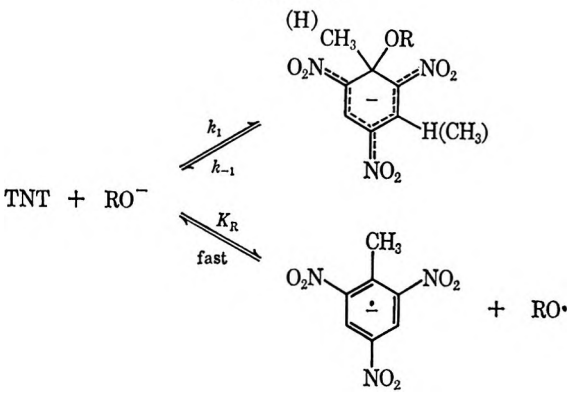
Though there is appreciable interference by τ_2 except at the highest three base concentrations used, τ_1 is much more easily measured in this system than it is in methanol; Figure 1d shows an oscilloscope trace at high base concentration. This is primarily due to the relative slowness of the reaction, which allows use of the stopped-flow technique instead of the temperature-jump technique and to the higher stability of the species giving rise to τ_1 in ethanol than in methanol.

As can be seen from the results in Table III, τ_1 not only depends on the concentration of the excess component (ethoxide) but on the TNT concentration as well. There are several possible interpretations for these observations. A Meisenheimer complex formation by attack of EtO^- on TNT coupled to a fast radical producing equilibrium, as shown in Scheme II, is the one we currently favor, though other possibilities can not be excluded by the data at hand.

If we assume that the equilibrium constant K_R for radical formation is small,[15] the τ_1 values allow crude estimates for k_1, k_{-1}, and K_1. These estimates are reported in the Discussion where it is shown that they are consistent with the hypothesis of Meisenheimer complex formation.

τ_2 was evaluated over a rather large range of ethoxide concentrations with the base in large excess. A plot

SCHEME II



of τ_2^{-1} *vs.* concentration is shown in Figure 4. Unlike the MeO^-/methanol system, the plot shows a definite downward curvature at high base concentration. Such curvature can be rationalized in terms of the fast preequilibrium giving rise to τ_1, the consequence of which is an expression of the form of eq 11, where

$$\frac{1}{\tau_2} = k_2[RO^-] \frac{1}{1 + f([RO^-])} + k_{-2} \qquad (11)$$

$f([RO^-])$ is a function of base concentration. The exact form of this function depends on the nature of the process responsible for τ_1. At low RO^- concentrations, $f([RO^-])$ becomes small compared to 1, so that eq 11 simplifies to eq 12, which is equivalent

$$\frac{1}{\tau_2} = k_2[RO^-] + k_{-2} \qquad (12)$$

to eq 5 under the conditions $[RO^-] \gg [TNT]$; k_2 and k_{-2} can be determined in the usual way from slope and intercept. They are reported in Table II.

τ_3 was determined in the temperature-jump apparatus with TNT as the excess component. The amplitudes displayed a similar behavior as in methanol. A plot of τ_3^{-1} *vs.* the TNT concentration is shown in Figure 3; it obeys eq 4. k_3 and k_{-3} were determined in the usual manner.

TNT and OH^- in 50% Dioxane–50% Water.—As in methanol and ethanol, temperature-jump and stopped-flow experiments showed the presence of three relaxation times. The data are summarized in Table IV. τ_2 and τ_3 are again attributed to the two processes

(15) This assumption seems justified because attempts to find independent evidence for radical formation have so far been inconclusive. No radicals can be detected by electron spin resonance in equilibrated reaction solutions, nor does the addition of 2-methyl-2-nitrosopropane, a well-known radical trapping agent,[16,17] have any effect on τ_1. However, there is a weak, slowly developing (several minutes after mixing) electron spin resonance signal characteristic of a nitroxide radical[17] when 2-methyl-2-nitrosopropane is added to the reaction solution.

(16) A. Mackor, Th. A. J. W. Wajer, and Th. J. De Boer, *Tetrahedron*, 1623 (1968).

(17) E. G. Janzen and R. J. Blackburn, *J. Amer. Chem. Soc.*, **90**, 5909 (1968).

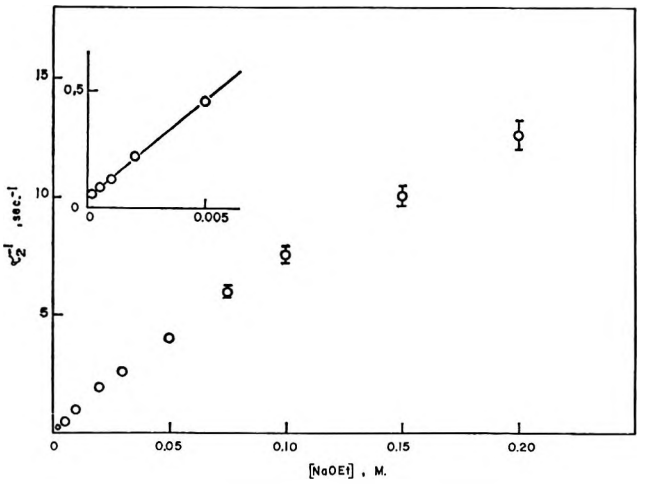


Figure 4.—Reaction of TNT with NaOEt in ethanol; τ_2^{-1} as function of [NaOEt].

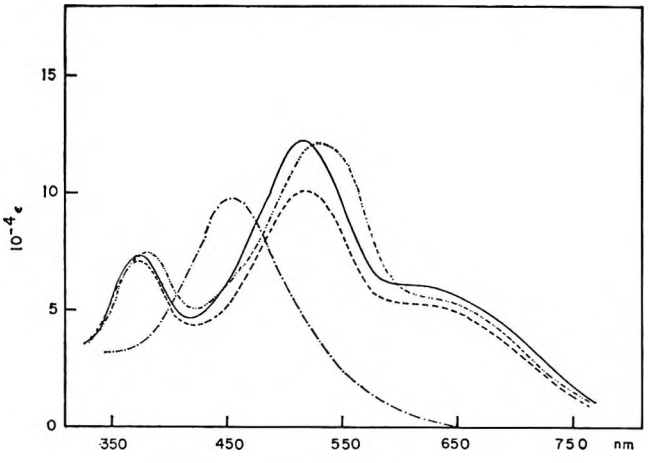


Figure 5.—Spectra of TNT^- in methanol (— — —), ethanol (———), and in 50% dioxane–50% water (—·—); spectrum of a solution of 10^{-3} *M* NaOH and 10^{-4} *M* TNT in 10% dioxane–90% (—·—). The units on the ordinate are arbitrary for the latter spectrum.

in Scheme I. τ_1, though more easily detectable than in methanol, could not be studied over an extended range of concentrations as in ethanol, due to strong interference with τ_2 under all practical conditions. A representative oscilloscope trace of τ_1 is shown in Figure 1e. τ_1 was evaluated by extrapolating the approximately straight second portion of the curve back to the zero and using this line as the infinity value for the superimposed exponential. There is considerable uncertainty in these τ_1 values, mainly because of some arbitrariness in the slope of the extrapolated lines.

In analogy to the ethanol system, τ_1 is tentatively attributed to Meisenheimer complex formation. The data do not allow a decision as to whether there is a radical-forming preequilibrium according to Scheme II.

τ_2 and τ_3 on the other hand are easy to measure. The values of τ_2 at the lowest base concentrations were determined by classical photometric methods. The percentage error for τ_2 is larger at low base concentrations due to interference with a slow unidentified side reaction. A plot of τ_2^{-1} *vs.* hydroxide concentration (not shown) is linear in accordance with eq 12, yielding k_2 and k_{-2}. Similarly, when τ_3^{-1} is plotted *vs.* TNT concentration, a straight line results (not shown) as

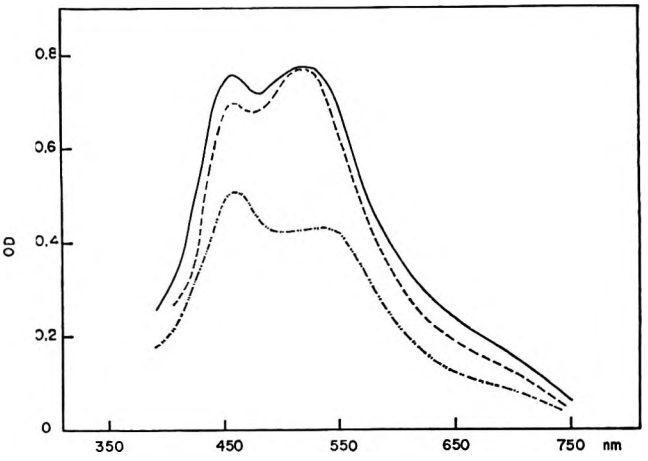


Figure 6.—Spectra of basic TNT solutions in various solvents: — — — in methanol (0.07 *M* TNT, 1.23×10^{-4} *M* NaOMe), ——— in ethanol (0.05 *M* TNT, 8.05×10^{-5} *M* NaOEt), —·— in 50% dioxane–50% water (0.02 *M* TNT, 6.60×10^{-5} *M* NaOH).

predicted by eq 4. The rate coefficients are summarized in Table II.

Spectra.—In Figure 5 spectra of TNT^- are shown in methanol, ethanol, and in 50% dioxane–50% water; they were calculated on the basis of spectra of TNT solutions with large excesses of base combined with our kinetically determined equilibrium data. The reliability of the extinction coefficients, which is affected by the limits of error in the kinetic determinations, by the absolute magnitude of K_2, and by the stability of the solutions toward slow decomposition, is estimated to be ±5% in ethanol and ±10% in methanol and in 50% dioxane.

In comparison, a spectrum of TNT in the presence of excess base in 10% dioxane–90% water is remarkably different and shows that a relatively minor change in medium has a significant effect on the chemistry of TNT. Though the species giving rise to this spectrum has not yet been identified, preliminary experiments in this laboratory indicate that radicals are formed, and that TNT^-, if formed at all, must be a very transient species.

Spectra where TNT is the excess component are shown in Figure 6. They are distinctly different from the spectra of TNT^-, owing to the contribution from JC. By means of eq 13, spectra of pure JC can be

$$\epsilon_{JC} = \frac{OD - \epsilon_{TNT^-}[TNT^-]}{[JC]} \quad (13)$$

calculated from the spectra in Figure 6; $[TNT^-]$ and [JC] are easily found from eq 14 and 15, where

$$[TNT^-] = \frac{K_2[TNT][RO^-]_0}{1 + K_2[TNT] + K_2K_3[TNT]^2} \quad (14)$$

$$[JC] = \frac{K_2K_3[TNT]^2[RO^-]_0}{1 + K_2[TNT] + K_2K_3[TNT]^2} \quad (15)$$

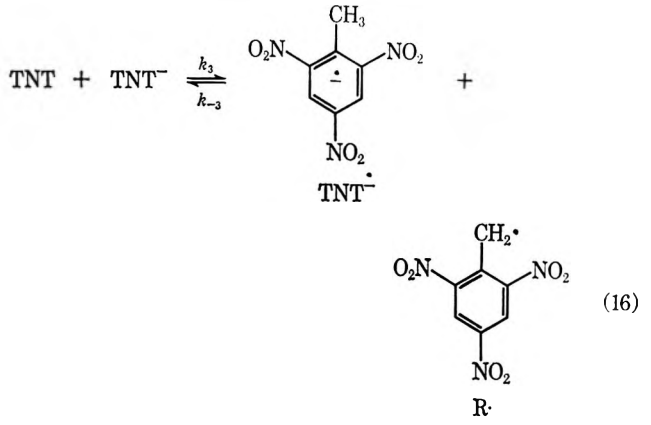
$[RO^-]_0$ is the "stoichiometric" concentration. $[RO^-]_0$, which was only in the order of 5×10^{-5} *M* to 10^{-4} *M*, had to be determined indirectly, due to possible error introduced by some absorbed CO_2. This was done by assuming that JC does not absorb above 680 mμ and that consequently all absorption above 680 mμ in Figure 6 is due to TNT^-. Thus by the ability to calculate the concentration of TNT^- from ϵ_{TNT^-}, $[RO^-]_0$ could be inferred indirectly; incidentally it

turned out that about 25% of the base had been neutralized by CO_2.

Calculated spectra of JC are shown in Figure 7; their uncertainty is estimated at ±20% due to the indirect multistep procedure of obtaining them. These spectra are characteristic of Janovsky complexes.[12,18]

Discussion

Evidence for TNT^- and JC Formation.—Direct structural proof through nmr spectroscopy is not feasible,[5,6] probably owing to the production of radicals which wipe out the spectrum.[5,6] In view of these reports,[5,6] of some of our own observations, and of findings by Russell and Janzen[19,20] that other nitrotoluenes easily undergo free-radical reactions in basic solution, the possibility that τ_3 might arise from reaction 16 instead of JC formation must be considered briefly. Reaction 16 requires τ_3 to be described by



(16)

eq 17 (instead of eq 3) which, under the condition

$$\frac{1}{\tau_3} = k_3([\mathrm{TNT}] + [\mathrm{TNT}^-]) + k_{-3}([\mathrm{TNT}^{\pm}] + [\mathrm{R}\cdot]) \quad (17)$$

$[\mathrm{TNT}] \gg [\mathrm{NaOR}]$, reduces to eq 18 (*cf.* eq 4). Taking

$$\frac{1}{\tau_3} = k_3[\mathrm{TNT}] + k_{-3}([\mathrm{TNT}^{\pm}] + [\mathrm{R}\cdot]) \quad (18)$$

into consideration that $[\mathrm{TNT}^{\pm}] = [\mathrm{R}\cdot]$ and expressing the radical concentrations in terms of reactant concentrations, eq 18 becomes eq 19. Equation 19

$$\frac{1}{\tau_3} = k_3[\mathrm{TNT}] + 2k_{-3}[\mathrm{TNT}]\sqrt{K_2K_3[\mathrm{RO}^-]} \quad (19)$$

predicts τ_3^{-1} to depend on the alkoxide ion concentration even when it is the minor component; it also requires a plot of τ_3^{-1} to go through the origin. This is contrary to experimental evidence (Tables I, III, and IV, Figure 3).

Our conclusion that τ_3 does not arise from radical formation does not exclude that reaction 16 is nevertheless a minor process undetected by our methods; the impossibility to take nmr spectra[5,6] and our esr experiments in ethanol does indeed suggest the interference by free radicals, either arising from reaction 16 or some other process.

As far as the evidence for TNT^- formation is concerned, our observation of a JC arising from the interaction of a second molecule of TNT with the primary

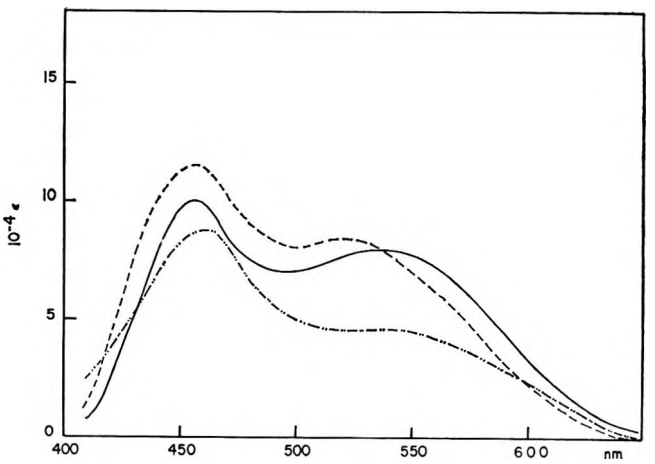


Figure 7.—Spectra of JC in methanol (— — —), ethanol (——), and in 50% dioxane–50% water (—··—).

product of the reaction between TNT and the lyate ion constitutes strong evidence that TNT^- is in fact this primary product in methanol, in ethanol, and in 50% dioxane–50% water. Such evidence is not available in 10% dioxane–90% water, and, in fact, the spectra in Figure 5 suggest that if TNT^- is present at all it is completely overshadowed by another species.

The results of our study in aqueous dioxane offer a possible interpretation for the apparently conflicting literature reports concerning hydrogen exchange. The Experiments of Bowden and Stewart[4] were performed in aqueous solutions containing 5–15 mol % of dimethyl sulfoxide.[21] Their solutions then were very aqueous and comparable to our 10% dioxane–90% water solution, which is confirmed by practically identical spectra of basic TNT solutions in the two media. As TNT^- plays only a very minor role if at all in these media, the insignificant hydrogen exchange reported by Bowden and Stewart finds a natural explanation.

On the other hand, when the water content of the mixed solvents is decreased, TNT^- apparently becomes the major species, as it does in methanol or ethanol, and the nearly complete rapid hydrogen exchange reported by Buncel,[3b] *et al.*, in 90% dimethylformamide–10% D_2O is easily rationalized.

Finally, findings of Miller and Wynne-Jones[3c] of a very slow exchange (23 atom % deuterium incorporated after 2–3 weeks in pyridine–D_2O with a very high pyridine content) can be understood by a consideration of the rate of TNT deprotonation. By extrapolating from k_2 in 50% dioxane–50% water, one can conclude that in such a weakly basic system the reaction must be very slow indeed, quite apart from the possible side reactions during this long period of time.

Kinetic and Equilibrium Data of TNT^- Formation.—A rate coefficient for TNT^- formation in ethanol[2a] as well as equilibrium constants in ethanol,[2a] in methanol,[22] and in ethylenediamine–water mixtures[23] has been reported previously. The agreement between the value of Caldin and Long[2a] for k_2 in ethanol and ours is very close, considering that their determination was made at 19.1°, and so is the agreement between the K_2 values in the same solvent. In methanol,

(18) C. A. Fyfe, *Can. J. Chem.*, **46**, 3047 (1968).
(19) G. A. Russell and E. G. Janzen, *J. Amer. Chem. Soc.*, **84**, 4154 (1962).
(20) G. A. Russell and E. G. Janzen, *ibid.*, **89**, 300 (1967).
(21) K. Bowden, personal communication.
(22) R. Schaal and G. Lambert, *J. Chim. Phys. Physicochim. Biol.*, **59**, 1151 (1962).
(23) R. Schaal, *ibid.*, **52**, 796 (1955).

the correspondence between K_2 of Schaal and Lambert[22] and ours is judged satisfactory.

It is interesting to note that the rate coefficients for deprotonation of nitroethane by MeO^- in methanol is 16.4 M^{-1} sec^{-1} and by EtO^- in ethanol is 88.2 M^{-1} sec^{-1} [24] which are practically the same for deprotonation of TNT. These very slow rates confirm the expectation that the proton transfer is accompanied by a significant electronic rearrangement and that the charge in TNT^- is strongly delocalized.

Janovsky Complex.—Though the spectra in Figure 7 are typical for a Janovsky complex,[12,18] it is not possible to decide whether the TNT^- has attached itself to the 1 or 3 position of TNT.

Rate and equilibrium constants (k_3, k_{-3}, and K_3) in methanol and ethanol are very nearly the same, which is reasonable for an isoelectronic reaction in two protic solvents differing only in their dielectric constant. k_2 in 50% dioxane is significantly higher than in the alcohols, which is most likely due to a lesser ground state solvation. The reverse rate is practically unaffected so that the equilibrium constant K_3 is larger by about the same amount as k_3.

Meisenheimer Complex.—A comparison of the crude estimates for k_1, k_{-1}, and K_1 with analogous data for MC formation[25] between 1,3,5-trinitrobenzene (TNB) and alkoxide ions is interesting. For TNB in ethanol $k_1 = 33400\ M^{-1}$ sec^{-1}, $k_{-1} = 27.5$ sec^{-1}, and $K_1 = 1210\ M^{-1}$ whereas for TNT $1500 < k_1 < 3000\ M^{-1}$ sec^{-1}, $80 < k_{-1} < 200$ sec^{-1}, and $7.5 < K_1 < 37.5\ M^{-1}$. In methanol $k_{-1} = 305$ sec^{-1} for TNB, whereas $600 < k_{-1} < 3000$ sec^{-1} for TNT if τ_1 is assumed to be mainly determined by k_{-1}.

The fact that $k_1^{TNT} < k_1^{TNB}$, $k_{-1}^{TNT} > k_{-1}^{TNB}$, and $K_1^{TNT} \ll K_1^{TNB}$ is consistent with the hypothesis of a Meisenheimer complex, because of the electron-releasing and steric[26] effects of the methyl group in TNT; it gives some support to our hypothesis.

Experimental Section

Materials.—2,4,6-Trinitrotoluene (Eastman White Label) was recrystallized twice from ethanol, mp 81–82°. Reagent grade methanol and ethanol were used without further purification. Stock solutions of NaOMe and NaOEt were prepared by dissolving sodium metal in the respective solvents under a stream of dry nitrogen. *p*-Dioxane was purified by the method of Fieser[27] and was stored over lithium aluminum hydride, from which it was distilled as needed. The 50% dioxane–50% water mixture was prepared by diluting 5 vol of dioxane to a total of 10 vol with distilled water. 2-Methyl-2-nitrosopropane was kindly provided to us by Dr. J. K. Kim. Where low base concentrations ($\leq 10^{-3}\ M$) were employed for kinetic or spectral determinations, carefully degassed solvents were used in order to minimize CO_2 interference.

Rate Measurements and Spectra.—The slow rates were measured on an automatized Kintrac VII[28] spectrophotometer at 450 mμ. Stopped-flow determinations were carried out on a Durrum[29] stopped-flow spectrometer between 425 and 500 mμ. The relaxation times listed in Tables III and IV represent average values of three to four single determinations. The temperature-jump experiments were done on a temperature-jump transient spectrometer from Messanlagen Gmbh.[30] Temperature jumps of 2° were applied. Relaxation times were determined at wavelengths between 415 and 585 mμ, depending on the optical density of the solutions. Each reported relaxation time represents the average of at least four relaxation curves. The electrolyte concentration was kept constant in the various series of runs by adding appropriate amounts of $NaClO_4$ or NaCl, respectively.

Spectra were taken on a Cary 14[31] uv spectrophotometer.

Registry No.—TNT, 118-96-7; MeO^-, 3315-60-4; EtO^-, 16331-64-9; HO^-, 14280-30-9.

Acknowledgment.—I am very thankful to Professor J. F. Bunnett for criticism and discussion, as well as to Dr. P. B. Chock for reading the manuscript.

Appendix

Amplitudes of Relaxational Processes.—The relative amplitude is defined as $\Delta OD/OD$ immediately following the temperature jump, *i.e.*, before reequilibration sets in. Under the assumption that only TNT^- and JC absorb,[32] the amplitude is given by eq 20

$$\frac{\Delta OD}{OD} = \frac{\epsilon_{TNT^-}\Delta[TNT^-] + \epsilon_{JC}\Delta[JC]}{\epsilon_{TNT^-}[TNT] + \epsilon_{JC}[JC]} \quad (20)$$

where $\Delta[TNT^-]$ and $\Delta[JC]$ are the displacement of the respective concentrations from their equilibrium value and $[TNT^-]$ and [JC] are the equilibrium concentrations.

A. Amplitude of τ_2 when $[RO^-] \gg [TNT]$.—Here [JC] and ΔJC are negligible compared to $[TNT^-]$ and ΔTNT^-. After a temperature jump the displacement of $[TNT^-]$ from its new equilibrium value is given by eq 21 for $\Delta K_2 \ll K_2$, where ΔK_2 is the

$$\Delta TNT^- = K_2[RO^-]\Delta TNT + \Delta K_2[RO^-][TNT] \quad (21)$$

change of K_2 as a consequence of the temperature jump. Substituting ΔTNT from the mass balance, eq 22, one obtains after some rearrangements eq 23.

$$\Delta TNT = -\Delta TNT^- \quad (22)$$

$$\Delta TNT^- = \frac{\Delta K_2[RO^-][TNT]}{1 + K_2[RO^-]} \quad (23)$$

$$[TNT^-] = K_2[RO^-][TNT] \quad (24)$$

Inserting eq 23 and eq 24 into eq 20 affords eq 7.

$$\frac{\Delta OD}{OD} = \frac{\Delta K_2}{K_2(1 + K_2[RO^-])} \quad (7)$$

B. Amplitude of τ_3 when $[TNT] \gg [RO^-]$.—In analogy to eq 21, ΔJC after a temperature jump is given by eq 25. The meaning of the subscript 3

$$\Delta JC_3 = K_3[TNT]\Delta TNT_3^- + \Delta K_3[TNT][TNT^-] \quad (25)$$

(24) P. Jones, J. L. Longridge, and W. F. K. Wynne-Jones, *J. Chem. Soc.*, 3606 (1965).

(25) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **92**, 4682 (1970).

(26) The steric effect can be visualized as hindrance to the attack by the nucleophile, if this attack is on the 1 position, though release of some steric strain between the methyl group and the two *o*-nitro groups by pushing the methyl group out of the plane of the benzene ring may partially compensate for that. If the attack is on the 3 position, steric strain may result from the interaction of the methyl group with the flanking nitro groups which have to be coplanar with the ring for an optimal delocalization of the negative charge.

(27) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 284.

(28) Beckman Instruments, Inc., Richmond, Calif.

(29) Durrum Instrument Corp., Palo Alto, Calif.

(30) Messanlagen Gmbh. Göttingen, Germany.

(31) Cary Instruments, Monrovia, Calif.

(32) MC, $TNT^{\pm}$, or whatever species accounts for τ_1 is present at too low concentration levels to significantly contribute to the overall optical density, whereas the absorption of TNT is negligible at the wavelength chosen.

in ΔJC_3 and ΔTNT_3^- is to refer to the displacement from the fast equilibrium, reaction 3, only. With the mass balance, eq 26, one arrives at eq 27. When

$$\Delta JC_3 = -\Delta TNT_3^- \quad (26)$$

$$\Delta TNT_3^- = -\frac{\Delta K_3[TNT][TNT^-]}{1 + K_3[TNT]} \quad (27)$$

eq 24, 26, 27, and 28 are inserted into eq 20, one obtains eq 9.

$$[JC] = K_3[TNT][TNT^-] \quad (28)$$

$$\frac{\Delta OD}{OD} = \frac{\Delta K_3[TNT](\epsilon_{JC} - \epsilon_{TNT^-})}{(1 + K_3[TNT])(\epsilon_{TNT^-} + \epsilon_{JC}K_3[TNT])} \quad (9)$$

C. Amplitude of τ_2 when [TNT] $\gg$ [RO$^-$].— In this situation ΔTNT_2^- and ΔJC_2 which refer to the equilibration of the slow reaction 2 are given by eq 29 and 30 where ΔTNT_{2+3}^- and ΔJC_{2+3} are the total displacement of the concentrations from the final equilibrium state. Note that

$$\Delta TNT_2^- = \Delta TNT_{2+3}^- + \Delta TNT_3^- \quad (29)$$

$$\Delta JC_2 = \Delta JC_{2+3} - \Delta JC_3 \quad (30)$$

$$\Delta JC_2 = K_3[TNT]\Delta TNT_2^- \quad (31)$$

because with respect to reaction 2 equilibrium 3 is always established. This simplifies eq 20 to eq 32.

$$\frac{\Delta OD}{OD} = \frac{\Delta TNT_2^-}{[TNT^-]} \quad (32)$$

ΔTNT_{2+3}^- and ΔJC_{2+3} are given by eq 33 and 34,

$$\Delta TNT_{2+3}^- = K_2[TNT]\Delta RO_{2+3}^- + \Delta K_2[TNT][RO^-] \quad (33)$$

$$\Delta JC_{2+3} = K_3[TNT]\Delta TNT_{2+3}^- + \Delta K_3[TNT][TNT^-] \quad (34)$$

whereas eq 35 holds for the mass balance. Combining

$$\Delta TNT_{2+3}^- + \Delta RO_{2+3}^- + \Delta JC_{2+3} = 0 \quad (35)$$

eq 33, 34, and 35, one gets eq 36. Thus by inserting

$$\Delta TNT_{2+3}^- = \frac{\Delta K_2[TNT][RO^-] - K_2\Delta K_3[TNT]^2[TNT^-]}{1 + K_2[TNT] + K_2K_3[TNT]^2} \quad (36)$$

eq 27 and 36 into eq 29 and dividing by [TNT$^-$], eq 32 becomes eq 8.

$$\frac{\Delta OD}{OD} = \frac{\Delta K_2}{K_2(1 + K_2[TNT] + K_2K_3[TNT]^2)} + \frac{\Delta K_3[TNT]}{(1 + K_3[TNT])(1 + K_2[TNT] + K_2K_3[TNT]^2)} \quad (8)$$

The Intermediacy of Phenylpropargylene and Phenylethynylnitrene[1]

R. SELVARAJAN AND J. H. BOYER*

Chemistry Department, University of Illinois, Chicago Circle Campus, Chicago, Illinois 60680

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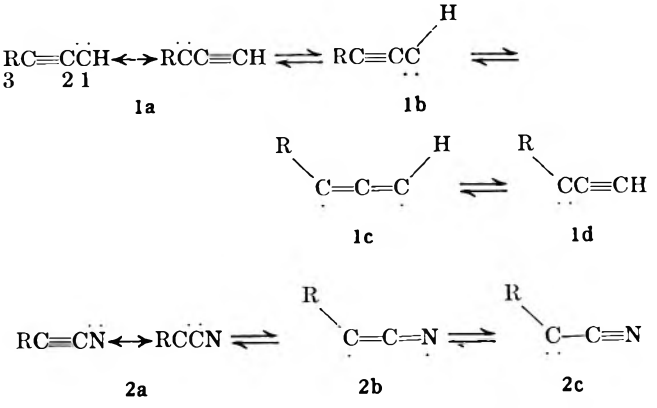
Diazomethane combines with phenylpropiolyl chloride to give 4-phenyl-1-diazo-3-butyn-2-one (**3**) and 3-chloroacetyl-4-phenylpyrazole (**4**). Phenylpropargylene (1a, R = C_6H_5), generated by irradiating the ketone **3**, abstracted hydrogen to produce benzylacetylene (**8**), phenylallene (**9**), and 1-methyl-2-phenylacetylene (**10**). Irradiation isomerized the allene **9** into the acetylene **8** but did not isomerize either of the acetylenes **8** and **10**. Phenylpropiolylcarbene (**5**) gave 4-phenyl-3-butyn-2-one (**7**) by hydrogen abstraction. A thermal Curtius reaction in different solvents transformed phenylpropiolyl azide (**11**) into phenylacetonitrile (**13**), but when the intermediate phenylethynyl isocyanate **12** was formed in aqueous ethanol it gave ethyl *N*-phenylacetylcarbamate (**15**) and *N,N'*-bisphenylethynylurea (**16**). A formal adduct between phenylpropiolylnitrene (**18**) and the isocyanate **12**, combined with ethanol, and subsequent isomerization gave 2-phenylethynyl-4- (or 5-) phenyl-5- (or 4-) carbethoxyaminooxazole (**17**) (tentative assignment). Irradiation of the azide **11** in methanol generated phenylethynylnitrene (2a, R = C_6H_5), which then reacted as phenylcyanocarbene (2a) to give α-methoxyphenylacetonitrile (**19**) by insertion and **13** by abstraction.

Centers of reactivity for propargylene (1, R = H) and ethynylnitrene (2, R = H) are displayed in formulas for respective resonance hybrids **1a** and **2a** and tautomers **1b–d** and **2b,c**; however, certain centers have such a low order of reactivity that they have not been detected. Propargylene and its methyl and phenyl derivatives, obtained by the photolysis of the appropriate diazopropyne, each showed electron paramagnetic resonance.[2] Triplet propargylene gave equal reactivity with olefins at C_1 and C_3. On the other hand, singlet propargylene reacted with olefins only at C_1, the position vacated by nitrogen.[2] Although phenylethynylnitrene (**2a**, R = C_6H_5) was presumed to have been initially formed from the irradiation of either phenylethynyl azide or phenylethynyl isocyanate, it reacted exclusively as phenylcyanocarbene (**2a**, R = C_6H_5).[3]

This report describes additional chemical properties pertaining to phenylpropargylene (**1a**, R = C_6H_5) and phenylethynylnitrene (**2a**, R = C_6H_5).



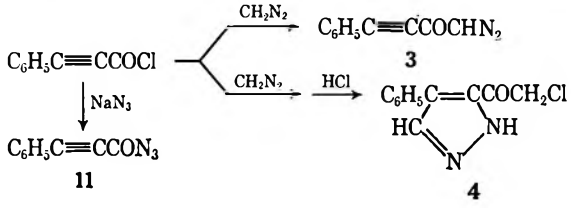
Diazomethane reacted with phenylpropiolyl chloride to give 4-phenyl-1-diazo-3-butyn-2-one (**3**) along with

(1) Financial support was received from NASA Grant No. NGR-14-012-004.

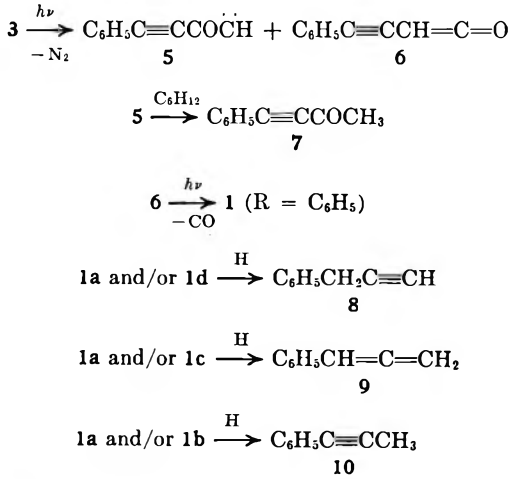
(2) R. A. Bernheim, R. J. Kempf, J. V. Gramas, and P. S. Skell, *J. Chem. Phys.*, **43**, 196 (1965).

(3) J. H. Boyer and R. Selvarajan, *J. Amer. Chem. Soc.*, **91**, 6122 (1969).

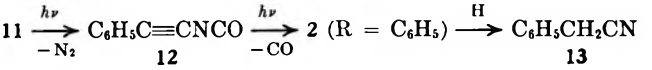
4-phenyl-5(3)-chloroacetylpyrazole (**4**).[4] Attempts to find optimum conditions for the formation of the ketone **3** were not made; however, to minimize the reaction between hydrogen chloride and the diazoacetyl function, an excess of diazomethane was present.



Irradiation of the diazo ketone **3** in cyclohexane brought about the elimination of nitrogen and left the residue both as unrearranged phenylpropiolylcarbene **5** and as the rearranged phenylethynylketene **6**. Isolation of phenylethynyl methyl ketone **7** offers diagnostic evidence for the intermediacy of the carbene **5** and its abstraction of hydrogen. Differentiation between a rearrangement of the carbene **5** and a rearrangement simultaneous with the release of nitrogen from **3** was not attempted. To account for the generation of phenylpropargylene (**1a**, R = C_6H_5), it is assumed that the undetected ketene underwent photoelimination of carbon monoxide. Again products of hydrogen abstraction confirmed the intermediacy of a carbene. Benzylacetylene (**8**) was generated from **1a** and/or **1d** (R = C_6H_5), while phenylallene (**9**) and methyl-2-phenylacetylene (**10**) were similarly generated from **1a** and/or **1c** and from **1a** and/or **1b** (R = C_6H_5), respectively. It was considered unlikely that either acetylene **8** or **10** could be the photo precursor of the other since independent irradiation of each did not bring about isomerization to a detectable extent. While photoisomerization of the allene **9** did afford benzylacetylene (**8**), not a trace of 1-methyl-2-phenylacetylene (**10**) could be found.[5] It is therefore concluded that the allene **9** could not be a required photo precursor of the acetylenes. It is of interest that products of carbene insertion into cyclohexane CH bonds were not found for either carbene **5** or **1** (R = C_6H_5); however, several minor products detected by gc have remained unidentified.



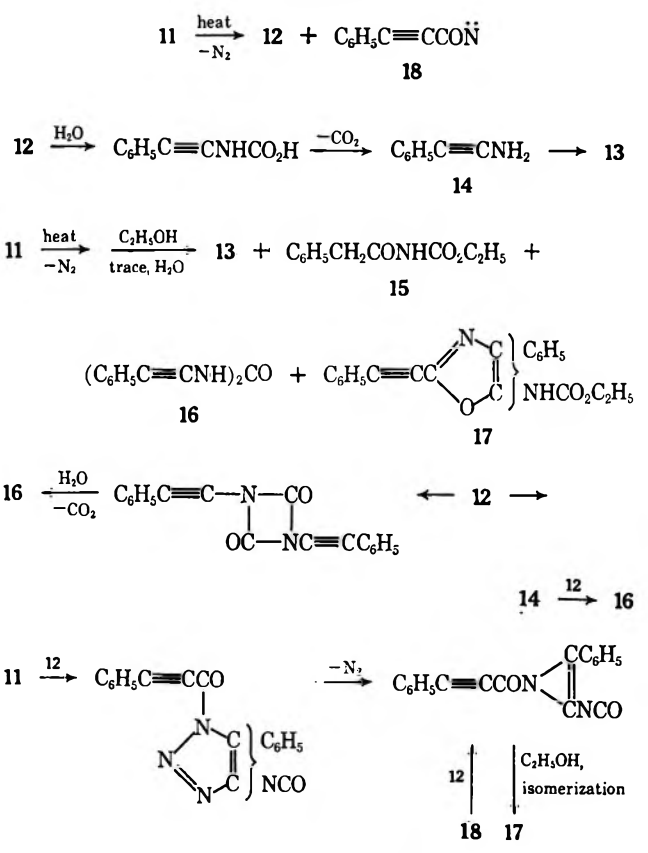
The photolysis of phenylpropiolyl azide (**11**) parallels the photolysis of the diazo ketone **3** insofar as the intermediacy of phenylethynyl isocyanate (**12**) and the ketene **6**, respectively, are required. Furthermore both intermediates apparently underwent photoelimination of carbon monoxide; however, the nitrene, produced from the isocyanate **12**, apparently reacted only as its isomer, phenylcyanocarbene (**2a,c**, R = C_6H_5).[3]



Further comparison between the diazo ketone **4** and the azide **11** was attempted by an investigation of their thermal reactions. When copper-catalyzed pyrolysis of the diazo ketone **3** gave only intractable material, this portion was dropped and the dark chemistry of the azide was reinvestigated.

Curtius and Kenngott obtained phenylacetonitrile (**13**) in unspecified low yield on pyrolysis of phenylpropiolyl azide in either dry ether, benzene, or carbon tetrachloride.[6] Without establishing the source of methylene hydrogen, they recognized that hydrolysis of isocyanate **12** followed by decarboxylation and tautomerization of phenylethynylamine (**14**) (Scheme I) could account for the product and, accordingly

SCHEME I



assumed the presence of trace amounts of water. In a similar reaction brought about by irradiation of phenylpropiolyl azide in anhydrous methylene chloride, the formation of phenylacetonitrile was attributed to hydrogen abstraction by phenylcyanocarbene.[3] Without

(4) A. Nabeya, F. B. Culp, and J. A. Moore, *J. Org. Chem.*, **35**, 2015 (1970), reported **4**, mp 185° (darkening). An ir spectrum (private communication) proved to be identical with the spectrum obtained in this work. See also A. Nabeya and J. A. Moore, *ibid.*, **35**, 2022 (1970).

(5) Photoisomerization of an allene had not been previously observed. D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967), discussed base-catalyzed and thermal (catalytic) isomerization of allenes into internal (disubstituted) acetylenes.

(6) Th. Curtius and E. Kenngott, *J. Prakt. Chem.*, **112**, 314 (1926).

invoking an unprecedented facile thermal elimination of carbon monoxide from an isocyanate, the present work supports the dark formation of phenylacetonitrile by the sequence of reactions initiated by hydrolysis of the isocyanate; however, the source of trace amounts of water was not established. Following pyrolysis of a 1% solution of the azide in anhydrous benzene and removal of excess solvent *in vacuo*, gc separation of the residue isolated the nitrile in 2.45% yield. A marked increase to 21.5% was established for the reaction of a 10% solution of the azide in benzene subsequently treated with ethanol after nitrogen evolution had ceased. A confirmation of the intermediacy of the isocyanate was found in the latter experiment in the formation of ethyl *N*-phenylacetylcarbamate (**15**) which required both hydration of the acetylenic function and addition of ethanol to the isocyanate function. Furthermore hydration of the isocyanate **12**, perhaps in the form of its uretidinedione dimer, is apparently required for the formation of *N*,*N*′-bisphenylethynylurea (**16**).[7]

Pyrolysis of phenylpropiolyl azide also gave a product tentatively assigned the structure of 2-phenylethynyl-4-(or 5-) phenyl-5- (or 4-) carbethoxyaminooxazole (**17**), which is supported by elemental analysis and nmr, ir, and mass spectra. Addition of either the azide **11** or the nitrene **18** to an acetylenic bond followed by nitrogen evolution if necessary and ring expansion through valence isomerization would account for its formation.

Failure to find either the carbamate **15**, or urea **16**, or oxazole **17** in the reaction mixture obtained by irradiation of phenylpropiolyl azide in methylene chloride[3] indicates that phenylethynylamine (**14**) was not formed. On the other hand, an unambiguous diagnostic test for intermediacy of phenylcyanocarbene is based on the formation of an insertion product. Photolysis of the azide **11** in methanol produced a mixture which contained α-methoxy-α-phenylacetonitrile (**19**), the result of carbene insertion into the methanolic hydroxyl bond. Methyl phenylpropiolate (**20**), produced by solvolysis of the azide **11**,[8] as well as phenylacetonitrile (**13**) and methyl phenylacetylcarbamate (**21**) were also found.

$$\mathbf{11} \xrightarrow[CH_3OH]{h\nu} \mathbf{13} + \underset{\mathbf{19}}{C_6H_5CH(CN)OCH_3} + \underset{\mathbf{20}}{C_6H_5C{\equiv}CCO_2CH_3} + \underset{\mathbf{21}}{C_6H_5CH_2CONHCO_2CH_3}$$

Experimental Section[9]

4-Phenyl-1-diazo-3-butyn-2-one.—A solution of phenylpropiolyl chloride[10] (8.2 g, 50 mmol) in diethyl ether (50 ml) was added dropwise to a stirred and cooled (5°) solution of diazomethane (6.0 g, 140 mmol) in ether (600 ml). After the solution was left overnight at room temperature, a clear yellow solution was separated from an unknown red resinous material by decantation and the solvent was removed under vacuum at 20°. A pale yellow residue (10.2 g) was purified by chromatography over a column of silica gel. A mixture, diethyl ether–petroleum ether, bp 30–60° (1:2, 1.2 l.), eluted pale yellow crystals of 4-phenyl-1-diazo-3-butyn-2-one (3.6 g, 42.5%): mp 54–54.5° (diethyl ether–petroleum ether, bp 30–60°); ν max (CCl_4) 2200 (s, C≡C), 2100 (vs, N_2), and 1615 cm^{-1} (vs, >C=O); λ max (MeOH) 218 nm (ε 14,290), 285 (16,630), and 307.5 (21,330); nmr ($CDCl_3$) δ 5.50 (s, broad, 1 H, O=CCHN$_2$) and 7.48 (m, 5 H, phenyl). *Anal.* Calcd for $C_{10}H_6N_2O$: C, 70.59; H, 3.53; N, 16.47. Found: C, 70.58; H, 3.63; N, 16.67.

Elution with a 1:1 mixture of diethyl ether–petroleum ether, bp 30–60° (1.2 l.), afforded colorless crystals of 3(5)-chloroacetyl-4-phenylpyrazole (1.25 g, 11.4%): mp 202–203° dec (ethyl acetate–hexane); ν max (KBr) 3230 (vs, broad, >NH), and 1680 cm^{-1} (vs, α,β-unsaturated carbonyl); nmr [$(CD_3)_2SO$] δ 5.12 (s, 2 H, O=CCH_2Cl), 7.50 (m, 5 H, phenyl), and 8.20 (s, 1 H, H-3(5)); mass spectrum *m/e* 222 and 220 (intensity ratio 1:3, M^+), 185 (M − Cl)$^-$, 171 (M − CH_2Cl)$^+$, 144, 143 (M − $COCH_2Cl$)$^+$, and 143 (M − C_6H_5)$^+$. *Anal.* Calcd for $C_{11}H_9N_2OCl$: C, 60.01; H, 4.09; N, 12.73. Found: C, 59.87, 59.86; H, 4.10, 4.15; N, 12.73.

Further elution with different solvents gave only an intractable resinous mixture.

Photolysis of 4-Phenyl-1-diazo-3-butyn-2-one in Cyclohexane.—A solution of the diazo ketone (0.68 g, 4 mmol) in anhydrous cyclohexane (200 ml) was irradiated at 300 nm while the reaction was monitored by ir. After 53 hr of irradiation the solution had turned dark brown and a coating had deposited on the walls of the reaction vessel. A weak ir absorption characteristic of the diazo function still persisted. The solution was concentrated under vacuum (45°) and the dark brown residue (0.43 g) was analyzed by gc (5% poly-*m*-phenyl ether, 6 ring, 6 ft by 0.25 in., 105°). Of the six volatile components three were identified, by comparison with their authentic gc retention times, to be benzylacetylene (trace), phenylallene (trace), and 1-methyl-2-phenylacetylene (3.66 mg, 0.95%, based on the recovered starting material).[11] Analysis by gc (Apiezon L, 10%) and mass spectra combination enabled identification of four components: 4-phenyl-3-butyn-2-one (**3**) (M^+ 144), benzylacetylene (**8**) (M^+ 116), phenylallene (**9**) (M^+ 116), and 1-methyl-2-phenylacetylene (**10**) (M^+ 116). The mass spectra of **8**, **9**, and **10** were identical.[12] Purification was attempted by chromatography over silica gel (12 in. × 1 in.). Elutions with a 1:1 mixture of hexane–benzene (1 l.) gave a pale yellow viscous liquid (21 mg): ν max (CCl_4) 2200 (s, C≡C), 1950 (m, >C=C=C<), 1750 (vs, >C=O), and 1680 cm^{-1} (s, >C=O); the presence of benzylacetylene, phenylallene, and 1-methyl-2-phenylacetylene was detected by gc.

Further elutions with benzene (400 ml) gave the unreacted 4-phenyl-1-diazo-3-butyn-2-one (110 mg, 16.2%). Elutions with different solvents afforded a dark brown resinous material which was not characterized further.

Photolyses of 1-Methyl-2-phenylacetylene, Phenylallene, and Benzylacetylene.—In quartz test tubes, solutions of 1-methyl-2-phenylacetylene[11] (80 mg, 0.69 mmol), phenylallene[11] (32.5 mg, 0.28 mmol), and benzylacetylene[11] (75 mg, 0.65 mmol) in anhydrous cyclohexane (18 ml) were separately irradiated at 300 nm under nitrogen while the reactions were monitored by gc. After 96 hr of irradiation the solutions were analyzed by gc (5% poly-*m*-phenyl ether, 6 ring, 6 ft × 0.25 in., 105°); unreacted 1-methyl-2-phenylacetylene (28 mg, 35%) and benzylacetylene (61 mg, 80%) but no isomerization of either was detected. The reaction mixture from phenylallene contained benzylacetylene (2.3 mg, 7.4%), unreacted phenylallene (4.6 mg, 1.47%), and an unidentified oil, apparently polymeric, which was the major component. Intractable material was found de-

(7) This appears to be the first example of a CNH atom sequence in which C is acetylenic. This assignment is based on ir, uv, nmr, and mass spectra and elemental analysis data (see Experimental Section). Tautomers, which require the presence of a ketenimine function, and nitrile isomers conceivably produced by rearrangement of ketenimines are not allowed by the data.

(8) Upon standing overnight cinnamoyl azide in ethanol gave ethyl cinnamate in a similar solvolysis.

(9) By flushing nitrogen for 12 hr the solvent was degassed in each case and photolyses were carried out at 35° under nitrogen in quartz vessels placed in Rayonet chamber reactor equipped with 16 low-pressure mercury lamps. Instrumental data were obtained from a Perkin-Elmer 237-B infrared spectrophotometer, a Cary-14 ultraviolet spectrometer, a Varian A-60A nmr spectrometer, and a Varian-Aerograph 1800 gas chromatograph. All yields are based on recovered starting material.

(10) Phenylpropiolyl chloride was obtained from Columbia Organic Chemicals Co., Inc., Columbia, S. C.

(11) Synthesis of benzyl acetylene following the procedure of J. R. Johnson and W. L. McEwen, *J. Amer. Chem. Soc.*, **48**, 469 (1926), led to a mixture of benzylacetylene, phenylallene, and trace quantities of two unidentified compounds. Preparative gc (30% SE-30, 20 ft × 0.37 in., 165°) gave pure samples of benzylacetylene (34%) and phenylallene (3.5%). 1-Methyl-2-phenylacetylene was commercially available.

(12) K. B. Wiberg, W. J. Bartley, and F. P. Lossing, *ibid.*, **84**, 3980 (1962). Propyne, allene, and cyclopropene gave identical mass spectra due to one common cation, $C_3H_3^+$, the structure of which is believed to be the cyclic and symmetrical cyclopropenylium cation.

posited on the walls of the reaction vessel in each of the three photolytic reactions.

Pyrolysis of a 1% Solution of Phenylpropiolyl Azide (11) in Benzene.—The pale yellow solution of the azide (1.02 g, 6 mmol) in anhydrous benzene (100 ml) was heated with stirring for 4 hr at 65°. The dark brown solution was evaporated to dryness under vacuum and the brown residue (0.99 g) was analyzed by gc over Apiezon L (15%) and Carbowax (15%) columns. Two volatile components in trace amounts and phenylacetonitrile (17.1 mg, 2.45%) were detected. The above residue was dissolved in 50 ml of ethanol (unknown water content) and refluxed for 2 hr and left standing overnight. The solvent was removed and the residue was chromatographed over silica gel (12 in. × 1 in.).

Benzene–chloroform mixtures (4:1 and 3:1, 200 ml each) eluted colorless crystals of *N,N'*-bisphenylethynylurea (16) (32 mg, 4.1%): mp 240–241°; ν max (KBr) 3480 and 3380 (s, >NH), 2200 (s, C≡C), 1625 (s, amide I), 1575 (s, amide II), and 1300 cm^{-1} (m, amide III); λ max (CH_3OH) 250 nm (ε 50,320) 297 (11,610), 310 (10,480), and 350 (11,290); nmr [$(CD_3)_2SO$] δ 7.35 (m, phenyl); mass spectrum *m/e* 260 (M^+), 259, 242 ($M - H_2O)^+$, 232 ($M - CO)^+$, 204 ($M - CO - N_2)^+$, 130 $(M)^{2+}$, 102 ($M - CO - N_2)^{2+}$, 78, and 77 $(C_6H_5)^+$. *Anal.* Calcd for $C_{17}H_{12}N_2O$: C, 78.47; H, 4.61; N, 10.77. Found: C, 78.42; H, 4.84; N, 10.53.

A benzene–chloroform mixture (1:1, 600 ml) eluted colorless crystals of 2-phenylethynyl-4(5)-carbethoxyamino-5(4)-phenyloxazole (17) (22 mg, 2.2%): mp 186–187°; ν max (KBr) 3500 (m, >NH), 2220 (m, C≡C), 1700 (s, amide I), 1575 (m, amide II), 1389, and 1314 cm^{-1}; λ max (CH_3OH) 228 nm (ε 37,390), 245 (44,230), 320 (10,030), 332 (10,030); nmr ($CDCl_3$) δ 1.15 (t, 3 H, CH_2CH_3), 4.00 (q, 2 H, OCH_2CH_3), 6.15 (broad, >NH), and 7.55 (m, 10 H, phenyl); mass spectrum *m/e* 332 (M^+), 288 ($M - CO_2)^+$, 287 ($M - OC_2H_5)^+$, 286 ($M - C_2H_5OH)^+$, 273 ($M - CO_2 - CH_3)^+$, 260 ($M - CO_2 - C_2H_4 - CO)^+$, 258 ($M - C_2H_5OH - CO)^+$, 243, 242, 241, 232, 230 ($M - C_2H_5OH - 2CO)^+$, 205, 204, 189 $(C_6H_5C{\equiv}CNHCO_2C_2H_5)^+$, 188, 127 $(C_6H_5C{\equiv}CCN)^+$, 102 $(C_6H_5C{\equiv}CH)^+$, 101 $(C_6H_5C{\equiv}C)^+$, 88 $(NHCO_2C_2H_5)^+$, and 77 $(C_6H_5)^+$. *Anal.* Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.82; N, 8.43. Found: C, 72.12; H, 4.85; N, 9.53.

Elutions with pure chloroform, ethyl acetate, and ethanol afforded a brown polymeric oil and a brown polymeric solid (220 mg) decomposing above 190°.

Pyrolysis of a 10% Solution of 11 in Benzene.—A solution of the azide (0.55 g, 3.21 mmol) in benzene (5 ml) was heated with stirring at 65–68° for 1 hr or until the evolution of nitrogen had ceased. After cooling to 25°, the reaction mixture was treated with absolute ethanol (10 ml) and refluxed for 2 hr. The solvent was removed and the black resinous residue was analyzed by gc (Apiezon L, 6 ft × 0.25 in., 180°). Phenylacetonitrile (81 mg, 21.5%) and an unidentified component were detected. Tlc (silica plates) with different eluents (benzene, chloroform, and ethyl acetate) established the presence of the oxazole 17, the urea 16, and two unidentified components. The above residue was chromatographed over silica gel (12 in. × 1 in.). Elutions with 4:1 and 3:1 mixtures of benzene–chloroform (800 ml) gave a mixture of two solids (56 mg) which upon sublimation [95–100° (0.2 mm)] gave colorless crystals of ethyl *N*-phenylacetylcarbamate (15) (24 mg, 3.8%) collected on the cold finger: mp 110–111°;[13] ν max (KBr) 3247 and 3175 (s, >NH), 1754 (s), and 1701 cm^{-1} (m, imide carbonyl); λ max (CH_3OH) 247 nm (ε 644), 252 (632), 258 (575), and 264 (433); nmr ($CDCl_3$) δ 1.28 (t, 3 H, CH_2CH_3), 4.06 (s, 2 H, $C_6H_5CH_2CO$), 4.22 (q, 2 H, $CH_3CH_2CO_2$), and 7.31 (s, 5 H, phenyl); mass spectrum *m/e* 207 $(M)^+$, 179 $(M - C_2H_4)^+$, 162 $(M - OC_2H_5)^+$, 161 $(M - C_2H_5OH)^+$, 135 $(M - C_2H_4 - CO_2)^+$, 117 $(M - C_2H_4 - CO_2 - H_2O)^+$, 116 $(C_6H_5CHCN)^+$, and 91 (tropylium)$^+$.

The residual solid left behind in the sublimation apparatus was crystallized twice from the chloroform–hexane mixture to give the oxazole 17 (26 mg, 4.8%), mp 186–187°. Further chromatographic elutions with pure chloroform and ethyl acetate gave a polymeric oil.

Photolysis of Phenylpropiolyl Azide 11 in Methanol.—Into anhydrous methanol (250 ml), degassed for 16 hr by flushing with nitrogen, the azide (1.02 g, 6 mmol) was added and the solution was irradiated at 300 nm under nitrogen for 7 hr with ir monitoring. The solvent was removed under vacuum and the brown residual viscous liquid (1.03 g) was analyzed by gc and gc–mass spectrum combination over SE-30 column (2.5%, 6 ft × 0.12 in., 100°). Of the four volatile components three were identified as phenylacetonitrile (4.98 mg, 0.71%, M^+ 117), α-methoxy-α-phenylacetonitrile (1.2 mg, 0.14%, M^+ 147), and methyl phenylpropiolate (M^+ 160). The residual product was chromatographed over silica gel (12 in. × 1 in.). A mixture of hexane–benzene (1:1, 400 ml) eluted a colorless liquid (160 mg) which upon fractionation by preparative gc (SE-30, 30%, 20 ft × 0.37 in., 225°) afforded methyl phenylpropiolate (60 mg, 6.3%): mp 25–26°; ν max (CCl_4) 2250 (vs, C≡C) and 1710 cm^{-1} (vs, >C=O); nmr (CCl_4) δ 3.80 (s, 3 H, CO_2CH_3) and 7.50 (m, 5 H, phenyl); mass spectrum *m/e* 160 (M^+).

A benzene–chloroform mixture (3:1, 1 l.) eluted colorless crystalline methyl phenylacetylcarbamate (21) (170 mg, 14.7%): mp 154–155°; ν max (KBr) 3247 and 3185 (m, >NH), 1754 (s), and 1684 cm^{-1} (m, imide carbonyl); λ max (CH_3OH) 247 nm (ε 448), 252 (434), 258 (388), and 263 (275); nmr (acetone-d_6) δ 3.73 (s, 3 H, CO_2CH_3), 4.00 (s, 2 H, $C_6H_5CH_2CO$), and 7.33 (s, 5 H, phenyl); mass spectrum *m/e* 193 (M^+), 161 ($M - CH_3OH)^+$, 118 $(C_6H_5CH{=}CO)^+$, and 91 (tropylium)$^+$. *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.70; N, 7.25. Found: C, 62.80; H, 5.79; N, 7.25.

Registry No.—**1a** (R = Ph), 28850-17-1; **2a** (R = Ph), 28861-28-1; **3**, 28861-29-2; **4**, 28861-30-5; **12**, 28861-31-6; **15**, 4283-15-2; **17**, 28850-18-2; **20**, 4891-38-7; **21**, 28861-34-9.

(13) S. Ruhemann and J. G. Priestly, *J. Chem. Soc.*, **95**, 449 (1909), reported mp 114–115°. Berger, F. Giagiu, Gh. Pollack, and C. Schonberger, *Lucr. P. Conf. Nat. Farm.*, 66 (1958) [*Chem. Abstr.*, **53**, 6213*d* (1959)], reported mp 106°.

Electrochemical Dimerization of 3-Methylcrotonaldehyde[1]

DAYTON MILLER, LEON MANDELL,* AND R. A. DAY, JR.

Department of Chemistry, Emory University, Atlanta, Georgia 30322

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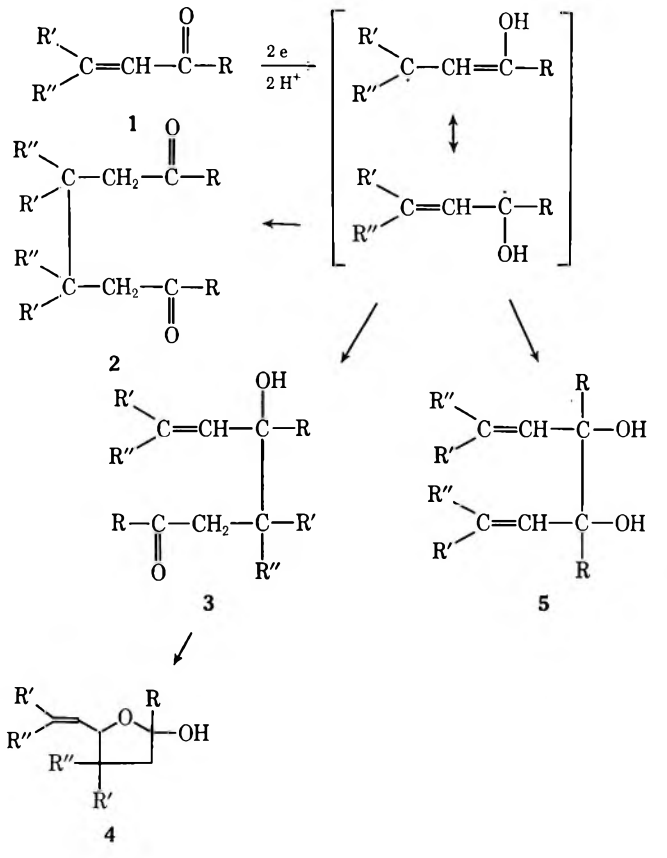
The electrochemical reduction of 3-methylcrotonaldehyde (**8**) was carried out at the controlled potential of −1.30 V in 0.25 *M* acetate buffer at pH 5.00 for the purpose of investigating this type of reduction as a possible synthetic tool for the preparation of dimeric glycols **5**. A 42% conversion to dimeric material was realized, which material consisted of three products. One was identified as the hydroxytetrahydrofuran **9** (67%), a second as the desired glycol **10** (24%), and the third product was tentatively assigned the structure **11** (9%).

The electrochemical reduction of α,β-unsaturated compounds (**1**) in aqueous media can yield, *a priori*, three different types of dimeric products (Scheme I):

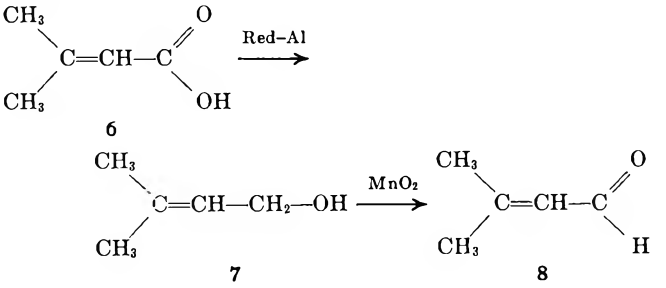
SCHEME I



a dicarbonyl compound (**2**), resulting from the coupling of two β radicals; a hydroxycarbonyl compound (**3**) [usually isolated as the hemiketal or hemiacetal (**4**)] from the "head to tail" coupling of a β radical and a carbonyl radical; and a glycol (**5**) from the coupling of two carbonyl radicals.

In most cases studied, the electrochemical reduction of α,β-unsaturated carbonyl compounds was found to lead to mixtures of dimeric products in which the diketone (**2**) was the major or only identifiable product.[2-4] However, there are several reports in the literature where electrochemical reduction affords dimeric glycols (**5**) as the major products. In these instances, the "R" attached to the carbonyl position is very small compared to the vinyl R′ and R″. The controlled potential reductions of crotonaldehyde,[4] prednisone, and cortisone[5] are excellent examples of such findings. This evidence appeared to point to the participation, at least in part, of steric control in determining the course of dimerization. If steric considerations were determined to be a prime controlling factor in these reactions, so that glycols could be produced exclusively in the reduction of β,β-disubstituted α,β-unsaturated aldehydes, then this could be a method of great synthetic utility, applicable to syntheses of many terpenes. For this reason, and the fact that no β,β-disubstituted α,β-unsaturated aldehydes had been investigated, we chose 3-methylcrotonaldehyde (**8**) as a model compound for this work.

Although 3-methylcrotonaldehyde (**8**) had been previously prepared by several different routes,[6] we deemed it more convenient to synthesize this aldehyde from the readily available carboxylic acid, 3-methylcrotonic acid (**6**), *via* the allylic alcohol (**7**). The carboxylic acid (**6**)



was therefore reduced with $NaAlH_2(OCH_2CH_2OCH_3)_2$ to 3-methyl-2-buten-1-ol, which was in turn oxidized to the desired aldehyde with activated manganese dioxide.[7]

The reduction potentials for this compound were determined by standard polarographic technique in acetate and phosphate buffers over the pH range 4–8. These values were normal (Table I), giving a roughly linear relationship of $E_{1/2}$ to pH.

The controlled potential reduction of the aldehyde was carried out under a nitrogen atmosphere in an electrolysis cell employing a stirred mercury pool cathode and a silver/silver chloride anode. Acetate buffer solution (0.25 *M*, pH 5.00) was used as the supporting electrolyte solvent system. Using a working potential of −1.30 V (at pH 5.00 $E_{1/2}$ = −1.27 V) the reduction of 500 mg of the aldehyde was complete within 2 hr.

(1) Taken from a portion of the Ph.D. dissertation of D. T. Miller, 1970.
(2) J. J. Lingane, "Electroanalytical Chemistry," 2nd ed, Interscience, New York, N. Y., 1958.
(3) R. Pasternak, *Helv. Chim. Acta*, **31**, 753 (1948).
(4) J. Wiemann and M. Paget, *Bull. Soc. Chim. Fr.*, 285 (1955).
(5) P. Kabasakalian and J. McGlotten, *J. Amer. Chem. Soc.*, **78**, 5032 (1956).
(6) (a) H. Normant, *Bull. Soc. Chim. Fr.*, 728 (1958); (b) K. Suga and Watanabe, *Hiroshima Daigaku Chigaku Kenkyu Hokoku*, **9**, 67 (1958); (c) J. R. Pollock, Ed., "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965.
(7) I. M. Goldman, *J. Org. Chem.*, **34**, 1979 (1969).

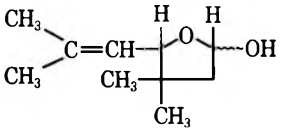
TABLE I

POLAROGRAPHY OF 3-METHYLCROTONALDEHYDE[a]

pH	$E_{1/2}$,[b] V	Buffer
4.00	−1.19	0.25 *M* acetate
5.00	−1.27	0.25 *M* acetate
6.00	−1.32	0.25 *M* acetate
7.00	−1.48	0.25 *M* phosphate
8.00	−1.49	0.25 *M* phosphate

[a] Aldehyde concentration 4.0×10^{-4} *M*. [b] Wave height was approximately 0.8 μA at all pH values.

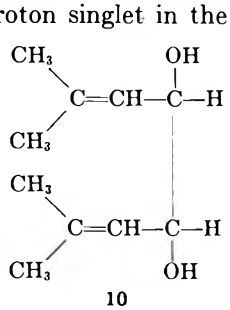
Extraction of the reaction mixture with ether yielded a pale yellow oil which was chromatographed on neutral silica gel, giving separation into three major chromatographic components totaling 211 mg, 42%. Positive structural assignments were made for two of these components and a tentative assignment was given to the third. The largest component, representing 67% of the total weight was identified on the basis of its ir, nmr, and mass spectral data as a mixture of the cis–trans isomers of the hydroxytetrahydrofuran derivative **9**. It exhibited a moderate hydroxyl absorption and a weak double bond absorption at 1700 cm^{-1}. Its nmr spectrum was most revealing. A six-proton doublet at 0.95 ppm (J = 7 Hz), and a six-proton doublet centered at 1.75 ppm (J = 4 Hz) were attributed to saturated gem methyls and gem vinyl methyls, respectively.



9

A broad one-proton singlet at 3.4 ppm was assigned to the hydroxyl proton. Two doublets (J = 9 Hz for both) integrating for one proton between them were centered at 4.4 and 4.7 ppm and were assigned to the proton on the carbon bearing the isobutene moiety, having slightly shifted resonances in the cis and trans isomers. These resonances appear as doublets because of coupling with the vinyl proton which shows up as a one-proton doublet centered at 5.15 ppm (J = 9 Hz). Finally, a broad one-proton triplet at 5.55 ppm (J = 6 Hz) was assigned to the proton on the carbon of the hemiacetal group.

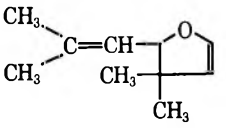
The next largest component was shown to be the desired glycol **10**, representing 24% of the total weight. Its ir spectrum showed the presence of strong hydroxyl absorption and moderate double bond absorption at 1700 cm^{-1}. The two sets of gem vinyl methyls appeared as a 12-proton singlet in the nmr at 1.7 ppm.



10

Both the vinyl protons and the protons on the carbons bearing oxygen appeared as two broad triplets integrating for two protons each. However, examination of early and late fractions of this chromatographic component revealed that these actually resulted from superimposed resonances attributable to the presence of both the *dl* and meso forms. Thus, one "apparent triplet" was actually two superimposed doublets centered at 5.1 and 5.25 ppm (J = 7 Hz) and was assigned to the vinyl protons. The other "apparent triplet" was shown to be two superimposed doublets of doublets centered at 4.15 and 4.3 ppm (J_1 = 7 Hz, J_2 = 2 Hz), and assigned to the protons on carbon bearing hydroxyl.

The smallest component represented only 9% of the reduction product. Its nmr spectrum (very dilute) was similar in many respects to that of **9**, and its ir spectrum was notable in that it lacked either hydroxyl or carbonyl absorption but did exhibit double bond absorption at 1720 cm^{-1}. It was tentatively assigned the dihydrofuran structure **11** based on this evidence.



11

On the basis of this work we must conclude that even in a very favorable case the carbonyl to carbonyl coupling is still only a secondary mode of reaction. This process then, would not seem to be of great synthetic promise for terpene synthesis.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian Model T-60 spectrometer in $CDCl_3$ solution using TMS as the internal standard. Ir spectra were taken on a Perkin-Elmer Infracord Model 137B in $CHCl_3$ solution. Mass spectra were obtained with a Varian Model M-66 mass spectrometer equipped with a peak matching device for precise mass measurements. Melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. A Leeds and Northrup 4701 pH meter was employed for pH measurements. The controlled potential electrolysis experiment was carried out using a Lingane–Jones potentiostat[8] in conjunction with an electrolysis cell having a stirred mercury pool cathode, a silver/silver chloride anode and a sce reference.

3-Methyl-2-buten-1-ol (7).—Under an atmosphere of N_2, 3-methylcrotonic acid (6) (50 g, 0.5 mol) was dissolved in 1 l. of dry benzene in a 3-l., three-neck round-bottom flask, fitted with a mechanical stirrer, reflux condenser, and a 500-ml constant-pressure addition funnel. The addition funnel was charged with 235 g (0.80 mol) of "Red-Al"[9] $[NaAlH_2(OCH_2CH_2OCH_3)_2]$ which was diluted with an additional amount of 200 ml of dry benzene. Stirring was begun and the metal hydride solution was added in a thin stream, while cooling with an ice bath, at such a rate as to maintain gentle reflux and moderate liberation of H_2. During the addition, which lasted about 1 hr, the solution became cloudy and finally set to a thick gel which resisted stirring but gradually became liquified. The solution was heated to reflux for an additional 30 min and then left stirring overnight at room temperature, after which time the solution was a clear bright gold color. The complex was decomposed by the dropwise addition of saturated NH_4Cl solution (about 200 ml) with cooling. The benzene solution was decanted and the aluminum salt residue was washed two times with 400 ml of ethyl ether. The organic extracts were combined, washed twice with H_2O, once with saturated NaCl, and dried over Na_2SO_4. Evaporation of the solvent gave 28 g crude alcohol containing some benzene. Distillation [52–55° (19 mm)] gave 16 g, 38% yield: nmr δ2.0 (d, 6 H) (J = 4 Hz), 2.9 (s, 1 H), 4.1 (d, 2 H) (J = 7 Hz),

(8) J. J. Lingane and S. L. Jones, *Anal. Chem.*, **22**, 1169 (1950).

(9) Red-Al is a trade name of the Aldrich Chemical Co. for a 70% solution of bis(2-methoxyethoxy)aluminum hydride in benzene.

5.4 (t, 1 H) (J = 7 Hz); ir (liquid film) 3300 (s), 2950 (s), 1690–1700 (w), 1450 (m), 1360 (m), 1100 (s), 1000 (s), 780 (w), 675 cm^{-1} (w).

3-Methylcrotonaldehyde (8).—Dry active MnO_2 (20 g) was prepared and activated in 200 ml of distilled benzene as reported by Goldman.[7] The alcohol **7** (2.0 g) was dissolved in 5 ml of benzene and added under N_2 with stirring to the activated MnO_2. The reaction was stirred at room temperature overnight. The suspension was filtered through Celite on a Büchner funnel and washed with ethyl ether, and the filtrate was evaporated to 1.0 g of a yellow oil showing nearly pure aldehyde by nmr, yield 50%: nmr δ 2.1 (d, 6 H) (J = 11.5 Hz), 5.9 (d, 1 H) (J = 8 Hz), 10.1 (d, 1 H) (J = 8 Hz); ir (liquid film) 2750 (m), 1680 (s), 1450 (m), 1360 (m), 1200 (m), 1120 (m), 1050 (m), 830 (m), 680 cm^{-1} (m). A semicarbazone derivative melted at 221–223° (lit.[6c] mp 221–222°).

Polarography of 3-Methylcrotonaldehyde (8).—The polarographic measurements were made on a L & N, Model 62200, Type E, recording polarograph using a standard dme and sce in a 10-ml polarographic cell. The solutions were purged with N_2 for 15–20 min prior to each run. The polarographic solutions, which were 4×10^{-4} M in aldehyde, were prepared by diluting to 25 ml, 2 ml of a 0.005 M stock solution of the aldehyde with the desired 0.25 M buffer solution, resulting in pH 4.00, $E_{1/2}$ = −1.19 V; pH 5.00, $E_{1/2}$ = −1.27 V; pH 6.00, $E_{1/2}$ = −1.32 V; pH 7.00, $E_{1/2}$ = −1.48 V; pH 8.00, $E_{1/2}$ = −1.49 V. The wave height was approximately 0.8 μamp at all pH values.

Controlled Potential Electrolysis of 3-Methylcrotonaldehyde (8).—The electrolysis was carried out with a Lingane–Jones[8] potentiostat in the electrolysis cell previously described. About 150 ml of pH 5.00, 0.25 M acetate buffer was placed in the cell over the pool of instrument grade mercury and purged with N_2 for 20 min. The cell was connected to the potentiostat and an initial background current was measured of 2 mA with an applied voltage of about 4 V and a reference to working electrode potential of −1.30 V. 3-Methylcrotonaldehyde (**8**), 0.50 g, in 10 cc of EtOH was then added dropwise at a rate such that the current limitations of the instrument were not exceeded (about 10 A). The electrolysis was complete within 2 hr as indicated by the return of the current to near the initial background value. The aqueous solution was extracted three times with ethyl ether, washed with saturated NaCl, and dried over Na_2SO_4. Evaporation of the solvent gave 0.53 g of a clear yellow oil, having a slight odor of acetic acid. Tlc analysis of this crude oil showed at least two mobile components when eluted with 50% ether–hexane (Eastman silica gel chromatograms). The entirec rude was chromatographed on 12 g of Silicar cc-7, eluting successively with hexane, benzene–hexane, benzene, ether–benzene, ether, ethanol, methylene chloride. Three major peaks were discernible, totaling 211 mg, 42%. The first peak, 18 mg, was eluted in 15% ether–benzene and was tentatively identified as the dihydrofuran derivative **11**. The second peak, 141 mg, eluted in 20% ether–benzene was identified as the hydroxytetrahydrofuran derivative **9**. The last significant peak, 52 mg, was eluted in 40% ether–benzene and was identified as the desired glycol (**10**). The evidence for these compounds is given below.

Component 1 (18 mg), 4,4-dimethyl-5-(2-methyl-1-propenyl)-dihydrofuran (11) (tentative): nmr δ 1.2 (d, 6 H) (J = 8 Hz), 1.7 (d, 6 H) (J = 4 Hz), 4.2 (d, 1 H), (J = 8 Hz), 5.15 (broad s, 1 H); ir 2900 (s), 1720 (w), 1690 (w), 1450 (m), 1370 (m), 1200–1050 (m), 1000 (s), 910 cm^{-1} (m).

Since **11** would obviously derive from the hydroxytetrahydrofuran derivative (**9**) by elimination of H_2O, an attempt at producing **11** from **9** by acid catalysis was made. Twenty milligrams of **9** (sublimed) was dissolved in 10 ml of dry benzene, a tiny crystal of p-toluenesulfonic acid was added, and the mixture was stirred at 45° for 12 hr under N_2. The benzene solution was then washed with H_2O, dried and evaporated, leaving a small amount of oil having a very sweet odor. Ir showed the loss of hydroxyl, and the presence of a double bond and carbonyl group. The nmr was weak and complex. The product may have been a mixture of **11** and a new aldehyde, produced by acid-catalyzed opening of the dihydrofuran system.

Component 2 (141 mg), 4,4-dimethyl-1-hydroxy-5-(2-methyl-1-propenyl)tetrahydrofuran (9): nmr δ 0.95 (d, 6 H) (J = 7 Hz), 1.75 (d, 6 H) (J = 4 Hz), 3.4 (s, 1 H), 4.4 (d, 0.25 H) (J = 9 Hz), 4.7 (d, 0.75 H) (J = 9 Hz), 5.15 (d, 1 H) (J = 9 Hz), 5.55 (t, 1 H) (J = 6 Hz); ir 3300 (w–m), 2900 (s), 1690 (w), 1450 (m), 1370 (m), 1140 (m), 1050 (m), 1005 (s), 950 (m), 910 cm^{-1} (m); mass spectrum, molecular ion at 170, intense peak at 85; precise mass 170.1313, corresponding to $C_{10}H_{18}O_2$.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.69; H, 10.62.

Component 3 (52 mg), 2,7-dimethyl-2,6-octadiene-4,5-diol (10): nmr δ 1.7 (s, 12 H), 4.15 (doublet of doublets) and 4.3 (doublet of doublets) both totaling 2 protons, (J_1 = 7 Hz, J_2 = 2 Hz for both), 5.1 and 5.25 (d, broad, 2 H total) (J = 7 Hz); ir 3500 (s), 3400 (s), 1660 (m), 1450 (s), 1380 (s), 1320 (m), 1230 (s), 1110 (s), 1040 (s), 1000 (s), 900 (w), 850 (m), 820 (m); mass spectrum, intense peak at 85 amu, no molecular ion.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.50; H, 10.56.

Registry No.—**7**, 556-82-1; **8**, 107-86-8; **9**, 28405-68-7; **10**, 28405-69-8.

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Condensation of Phenylhydroxylamine with Hydroxymethylenedesoxybenzoin

D. J. WOODMAN,* N. TONTAPANISH, AND J. V. VAN ORNUM

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

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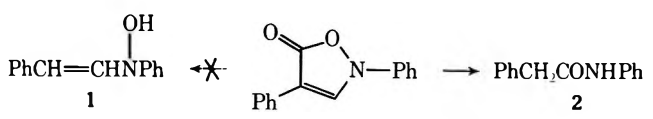
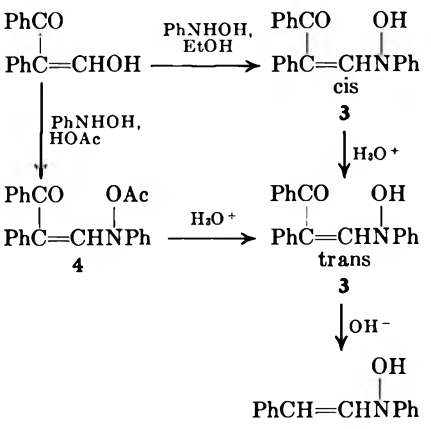
The reaction of phenylhydroxylamine with hydroxymethylenedesoxybenzoin has been shown to give derivatives of benzoylphenylacetanilide rather than the previously reported vinylhydroxylamines.

The recent finding that the postulated N-phenyl-N-styrylhydroxylamine (1) from the reaction of a 3-isoxazolin-5-one with aqueous base[1] is actually phenylacetanilide (2)[2,3] led us to reexamine the structure of other reported[4] vinylhydroxylamines from the condensation of phenylhydroxylamine with hydroxymethylenedesoxybenzoin. The reported[4] series of transformations summarized in Scheme I was of interest since the hydrolysis of the compound assigned the structure of the trans isomer of **3** had been cited in support of the incorrect structure **1**. When the hydrolysis product had been shown instead to be **2**, DeSarlo and Renzi proposed[2] that the precursor was benzoylphenylacetanilide (**5**) rather than **3** and suggested that a rearrangement might be responsible for the formation of **5**.



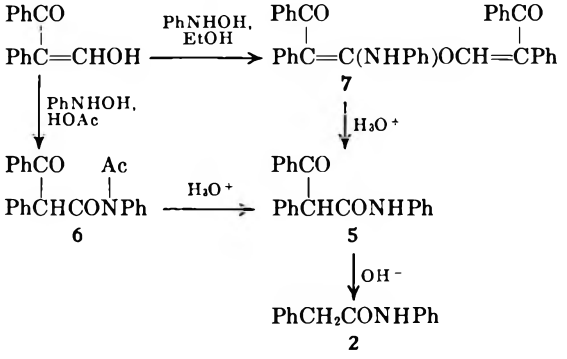
(1) H. Rupe and J. Grünholz, *Helv. Chim. Acta*, **6**, 102 (1923).
(2) F. DeSarlo and G. Renzi, *Tetrahedron*, **22**, 2995 (1966).
(3) D. J. Woodman, C. H. Borman, N. Tontapanish, and P. M. Stonebraker, *J. Org. Chem.*, **34**, 2981 (1969).
(4) H. Rupe and W. Wittwer, *Helv. Chim. Acta*, **5**, 205 (1922).

SCHEME I



Our investigation has confirmed that the compound previously thought to be the "trans" vinylhydroxylamine **3** is in fact benzoylphenylacetanilide (**5**). In addition the earlier structural assignments of **4** and the "cis" isomer of **3** also have been found to be incorrect. The actual structures are **6** and **7**, respectively, as shown in Scheme II.

SCHEME II

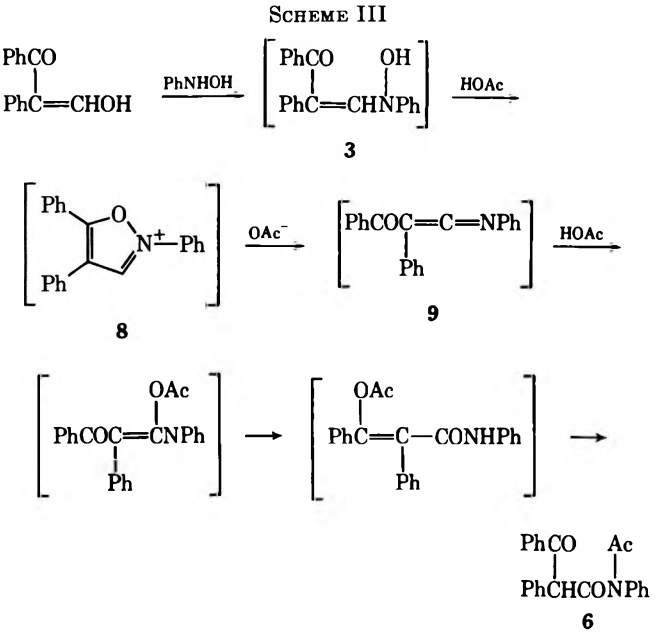


The addition of phenylhydroxylamine to a solution of hydroxymethylenedesoxybenzoin in glacial acetic acid afforded in low yield crystals having the same properties and elemental analysis as reported[4] by the earlier workers. However, the absence of long wavelength absorption in the ultraviolet spectrum indicated the compound lacked the conjugated chromophore of the proposed structure **4**. The spectral characteristics were in accord with the alternative structure of an *N*-acetyl derivative (**6**) of benzoylacetanilide.

A likely pathway to the diacylamide **6** is given in Scheme III. Although an initial condensation presumably gives the vinylhydroxylamine **3**, it apparently cyclizes to the isoxazolium cation **8** in acetic acid solution. Vinylogous hydroxamic acids closely related to the structure **3** are known to undergo this type of cyclization in the presence of acid.[5,6] The possibility of a facile cyclization with this system under conditions of moderate acidity was confirmed by the isolation of the perchlorate salt of the cation **8** from a mixture of hydroxymethylenedesoxybenzoin, phenylhydroxylamine, and perchloric acid in ether. The cyclization of **3** in acetic acid would produce an equivalent of acetate ion, and the reaction of 3-unsubstituted cations such as **8**

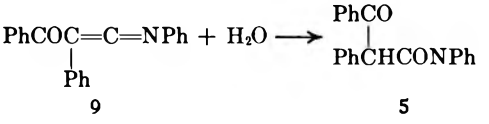
(5) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **31**, 2039 (1966).
(6) D. J. Woodman and Z. L. Murphy, *ibid.*, **34**, 1468 (1969).

SCHEME III

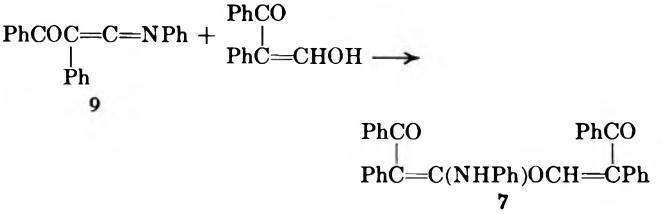


with carboxylate ions to give diacylamides by the sequence of transformations in Scheme III is well established.[7,8] In confirmation of the structural assignment of the diacylamide **6**, an authentic sample, prepared *via* this route by treatment of the isoxazolium (**8**) perchlorate with triethylammonium acetate, was found to be identical with the material from the condensation reaction in acetic acid.

Similarly, duplication of the procedures reported[4] to give the "trans" isomer of the vinylhydroxylamine **3** gave instead a compound with the spectral properties expected for benzoylphenylacetanilide (**5**). The identity of **5** also was confirmed by comparison with an authentic sample, prepared by the hydration of the acylketenimine **9**.



Finally, in our hands the condensation in ethanol gave a small amount of solid which underwent the reactions reported[4] for the postulated cis isomer of **3**, but the elemental composition of the material differed from that found by the previous workers. Our analyses indicated the combination of phenylhydroxylamine with two equivalents of the carbonyl compound. In this case again it appears that cyclization to **8** and ring opening have taken place, since we obtained the identical compound by addition of hydroxymethylenedesoxybenzoin to the acylketenimine **9**. While the spec-



(7) R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron Suppl.*, **7**, 415 (1966).
(8) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

tral properties are in agreement with the simple adduct **7**, the possibility of migrations of the PhCOC(Ph)=CH— group to give some other derivative of **5** from **7** cannot be excluded on the basis of our data.

Experimental Section

2,4,5-Triphenylisoxazolium Perchlorate (8).—A mixture of 2.41 g (10.8 mmol) of hydroxymethylenedesoxybenzoin and 1.21 g (11.1 mmol) of *N*-phenylhydroxylamine in 75 ml of dry ether was stirred vigorously with protection from light while 1.5 ml of 70% $HClO_4$ was added dropwise. Stirring was continued several hours, and the solution was stored overnight in a refrigerator. The next day a dark precipitate was removed by filtration, washed with ether, and dried. Precipitation of the crude product from acetone with ether gave 2.52 g (59%) of solid: mp 137–138° dec; uv $\lambda_{max}^{0.1\ M\ HCl}$ 250 mμ (ε 15,700) and 333 (3000); nmr (MeCN) τ 0.26 and aromatic signals centered at τ 2.4.

Anal. Calcd for $C_{21}H_{16}ClNO_5$: C, 63.36; H, 4.03; Cl, 8.94; N, 3.52; O, 20.14. Found: C, 63.24; H, 4.13; Cl, 8.81; N, 3.65; O, 20.19.

Benzoylphenylacetanilide (5).—A suspension of 0.201 g (0.5 mmol) of the perchlorate of **8** in water containing excess (0.2 ml) triethylamine was stirred 2 hr with warming in a hot-water bath, giving a yellow solid which was removed by filtration. One recrystallization from acetic acid followed by two recrystallizations from ethanol–water gave 0.117 g (73.5%) of **5**: mp 170–171° (lit.[4] 166°); ir (KBr) 3.07 (NH), 5.98 (C=O), 6.02 (amide I), 6.47 (amide II) μ; uv λ_{max}^{MeCN} 228 mμ; nmr τ 4.33 (s, 1.0), 2.57 (s, 10.0), and 0.70 (br, 0.99).

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44; O, 10.15. Found: C, 79.84; H, 5.49; N, 4.56; O, 10.11.

***N*-Acetylbenzoylphenylacetanilide (6). Preparation from Hydroxymethylenedesoxybenzoin.**—To a solution of 0.224 g (1.00 mmol) of hydroxymethylenedesoxybenzoin in 0.2 ml of glacial acetic acid was added in portions 0.122 g (1.12 mmol) of phenylhydroxylamine. The brown solution was stirred for 2–3 hr, warmed briefly, and partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4) and evaporated. Recrystallization of the residue first from ethanol and then from benzene gave 0.082 g (23%) of **6**: mp 158–160° (lit.[4] 157–158°); ir (KBr) 5.86, 5.99, and 6.27 μ; uv λ_{max}^{MeCN} 245 mμ (ε 15,800); nmr τ 7.93 (s, 3.04), 3.45 (s, 0.97), and 2.72 (s, 10.00).

Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.28; H, 5.36; N, 3.92; O, 13.44. Found: C, 77.21; H, 5.48; N, 4.07; O, 13.24.

Preparation from the Perchlorate of 8.—Excess (0.15 ml) Et_3N was added dropwise to a suspension of 0.203 g (0.51 mmol) of the perchlorate of **8** in cold CH_2Cl_2. Immediately excess (0.2 ml) HOAc was added dropwise to the stirred solution over a period of 15 min and the solution was stirred for 4 hr. The solution was diluted with an equal volume of benzene, partially evaporated to precipitate the bulk of the triethylammonium salts, and partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4) and evaporated. Recrystallization of the residue from ethanol gave 0.120 g (66%) of **6**, having melting point and mixture melting point identical with that of **6** above.

Hydrolysis of 6 to 5.—A mixture of 0.127 g (0.36 mmol) of **6**, and 10 drops of concentrated H_2SO_4 in 10 ml of EtOH was heated under reflux overnight. A solid precipitated upon dilution with an equal volume of water. Recrystallization from EtOH–water gave 0.042 g (37%) of **5**, having melting point and mixture melting point identical with that of **5** above.

Condensation of Phenylhydroxylamine and Hydroxymethylenedesoxybenzoin.—Phenylhydroxylamine, 0.091 g (0.84 mmol), was added in portions over a period of 14 min to a suspension of 0.177 g (0.79 mmol) of hydroxymethylenedesoxybenzoin in 3 ml of absolute EtOH in a dry reaction vessel. Stirring the mixture for 5–6 hr produced a milky yellow solution. Evaporation of the solvent and recrystallization of the residue from benzene gave 0.068 g (17%) of solid: mp 164–166°;[9] ir (KBr) 3.06 (NH), 6.08, 6.20, and 6.52 μ; uv λ_{max}^{MeCN} 354 mμ (ε 13,600); nmr τ 2.93 (25) and −0.32 (s, 1).

Anal. Calcd for $C_{36}H_{27}NO_3$: C, 82.89; H, 5.22; N, 2.69; O, 9.20. Found: C, 83.12, 83.08; H, 5.36; 5.30; N, 2.68, 2.66; O, 9.07, 9.08.

Reaction of Hydroxymethylenedesoxybenzoin, Triethylamine, and the Perchlorate of 8.—To a solution of 0.402 g (1.01 mmol) of the perchlorate of **8** in CH_2Cl_2 was added dropwise an excess (0.25 ml) of triethylamine. A dark reddish brown solution was obtained after stirring for 3–4 hr. Triethylammonium perchlorate was precipitated by repeated dilution with an equal volume of benzene, partial evaporation, and decantation. Hydroxymethylenedesoxybenzoin, 0.228 g (1.02 mmol), was added to the cold benzene solution, and the mixture was allowed to stand overnight in a refrigerator. Filtration, washing the solid with benzene, and air-drying gave 0.295 g (56%) of material having melting point and mixture melting point identical with that of the above product.

Registry No.—**5**, 22468-40-2 **6**, 28478-23-1; **8**, 28537-45-3; phenylhydroxylamine, 100-65-2; hydroxymethylenedesoxybenzoin, 28478-24-2.

(9) The reported[4] melting point (158°) was obtained for the crude product. The compound underwent thermal decomposition to an uncharacterized compound of the same melting point and elemental analysis as reported by the previous workers.

Conformational Analysis. LXXV. The Methylation Rates of *cis*- and *trans*-4-*tert*-Butyl-*N*,*N*-dimethylcyclohexylamines[1,2]

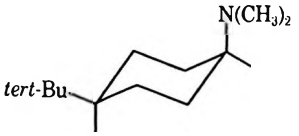
NORMAN L. ALLINGER[3] AND JOHN C. GRAHAM

Departments of Chemistry, Wayne State University, Detroit, Michigan 48202, and University of Georgia, Athens, Georgia 30601

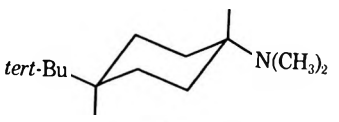
Received December 3, 1970

The rates of methylation of *cis*- and *trans*-4-*tert*-butyl-*N*,*N*-dimethylaminocyclohexane have been measured as functions of temperature, and the trans reacts about 50 times faster. The activation enthalpies are similar (10.1 kcal/mol for trans and 9.2 for cis), but the activation entropies differ considerably (−29.6 eu for trans and −40.3 for cis). The data suggest that the structures of the stereoisomeric 4-methyl-*N*,*N*-dimethylaminocyclohexanes were incorrectly assigned and that the *cis*-4-*tert*-butyl-*N*,*N*-dimethylaminocyclohexane reacts through a chair conformation and not a boat as previously suggested.

Although there are many literature references regarding rates of saponification and esterification at groups exocyclic to cyclohexane rings,[4] prior to the beginning of this investigation there was no available information regarding the rates of alkylation of simple, conformationally stable exocyclic amines.[5,6] In this work, the rates of methylation of *cis*- and *trans*-4-*tert*-butyl-*N*,*N*-dimethylcyclohexylamines (I and II) in acetonitrile were determined at various temperatures.

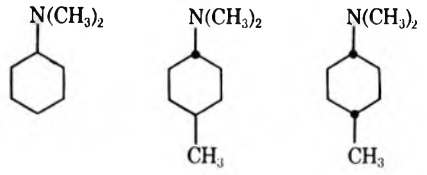


I



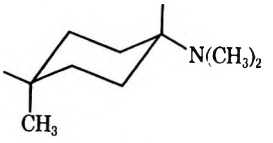
II

Peeling and Stone,[7] in a short communication, reported the second-order rate constants for the methylation of the isomeric methyl-*N*,*N*-dimethylcyclohexylamines with iodomethane at 40°. The following data are reproduced from their publication.

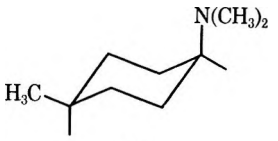


	III	IV	V
k_2 (mol^{-1} min^{-1}) at 40°	3.11	2.4	3.2

From a consideration of some of the principles of conformational analysis,[1] these data are quite surprising. It is now clear[4] that the cis isomer V is not conformationally rigid as was assumed by these authors, and it will exist as a mixture of two conformers V_e and V_a, one in which the amine group is equatorial and one in which the amine group is axial. Sicher and coworkers[8] have determined from pK_a measurements a conformational free energy of 2.1 kcal/mol for the dimethylamino group. Using this value, together with the average value reported for the conformational free energy of the methyl group in solution (1.7 kcal/mol[9]) one calculates that the equilibrium mixture at 0° will contain 65% V_e and 35% V_a. Since it may be assumed



V_e



V_a

that V exists to an appreciable extent as conformer V_a where the dimethylamine group is axial, and since it is known experimentally that axial groups undergo reactions at reduced rates when compared to equatorial groups in cases in which the congestion increases in the product (and hence transition state) relative to the starting material,[10-13] V would be expected to undergo methylation at a slower rate than the trans isomer IV. The implication, then, is that in this particular reaction the axial amine alkylates more rapidly than the equatorial. Alternatively, Peeling and Stone may have assigned the configurations of the amines incorrectly (no details given), assuming their work is otherwise valid.

In the present work, we have studied the conformationally well-defined 4-*tert*-butyl-*N*,*N*-dimethylcyclohexylamines to see if the unexpected implication of the work of Peeling and Stone can be verified. Winstein and Holness[14] have established that the 4-*tert*-butyl-substituted cyclohexane ring is conformationally biased to the extent that it is ordinarily conformationally pure. By utilizing the 4-*tert*-butyl-substituted isomers, rates of reactions can be measured on the separate equatorial and axial substituents. Kinetic data gathered in this manner are valid for interpreting the data on the unsubstituted compound only if the 4-*tert*-butyl group does not change the reactivity of the compound relative to the cyclohexyl system by either steric or electronic interaction. Evidence which indicates that this assumption is a good approximation has been gathered by a

(1) Paper LXXIV: N. L. Allinger, J. J. Maul, and M. J. Hickey, *J. Org. Chem.*, in press.

(2) This work was supported in part by Grant GP 15263 from the National Science Foundation.

(3) Correspondence concerning this work should be directed to this author at the University of Georgia.

(4) For leading references, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965.

(5) After this work was completed, a paper by Sicher and coworkers[6] was published on the same subject.

(6) J. Sicher, M. Tichý, J. Závada, and J. Krupička, *Collect. Czech. Chem. Commun.*, **33**, 1438 (1968).

(7) E. R. A. Peeling and B. D. Stone, *Chem. Ind. (London)*, 1625 (1959).

(8) J. Sicher, J. Jonáš, and M. Tichý, *Tetrahedron Lett.*, 825 (1963).

(9) J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967, p 204.

(10) Reference 4, p 72 ff.

(11) E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Amer. Chem. Soc.*, **83**, 2351 (1961).

(12) N. B. Chapman, R. E. Parker, and P. J. A. Smith, *J. Chem. Soc.*, 3634 (1960).

(13) J. L. Mateos, C. Perez, and H. Kwart, *Chem. Commun.*, 125 (1967).

(14) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

number of investigators;[15] however, some recent work has been critical of this approach.[16,17]

In the present work, the known *cis*- and *trans*-4-*tert*-butyl-*N*,*N*-dimethylcyclohexylamines (I and II) have been prepared. The pseudo-first-order rate constants for methylation in acetonitrile when the system was flooded with methyl iodide have been measured by means of a conductimetric bridge. The validity of this method has been previously established in amine systems.[18,19] The mathematics used is that applied by Shamma and Moss.[18,20]

Results

The results of the methylation of *cis*- and *trans*-4-*tert*-butyl-*N*,*N*-dimethylcyclohexylamines (I and II) are reproduced in part in Table I (complete data are given in Table II).

First it may be noted that the trans isomer reacts some 50 times as rapidly as the cis at the same temperature. This is as one would suppose, and it casts grave doubt on the work of Peeling and Stone. The rates independently determined by Sicher[6] are in good agreement with ours. Sicher found rates of 1.52 and 78.30 (10^{-3} mol^{-1} sec^{-1}) at 20° for *cis*-I and *trans*-II, and our corresponding numbers, extrapolated and interpolated to 20°, are 1.41 and 78.77, respectively. Sicher measured rates at only one temperature and hence could determine the free energy of activation ($\Delta G^{\pm}$) but not the corresponding enthalpy ($\Delta H^{\pm}$) or entropy ($\Delta S^{\pm}$) for the reactions.[6] He discussed the possibility of the cis isomer proceeding through a transition state in which the ring was in a boat conformation but had no evidence on the point. Since we measured the rates as a function of temperature, we were able to draw further conclusions in this regard.

The free energy of activation ($\Delta G^{\pm}$) was calculated according to the following equations

$$\Delta G^{\pm} = -RT \ln K^{\pm}$$

$$K^{\pm} = k_2 h / k_b T$$

where k_2 is the second-order rate constant as found in Table I, h is Planck's constant equal to 6.625×10^{-27} erg sec, k_b is the Boltzmann constant equal to 1.38×10^{-16} erg/°K, and T is the absolute temperature. The enthalpy ($\Delta H^{\pm}$) and the entropy ($\Delta S^{\pm}$) were calculated from the following

$$\Delta G^{\pm} = \Delta H^{\pm} - T\Delta S^{\pm}$$

and since $\Delta G^{\pm} = -RT \ln K^{\pm}$, $-\ln K^{\pm} = +\Delta H^{\pm}/RT - \Delta S^{\pm}/R$. The least-squares line was fitted to the variation of $-\ln K^{\pm}$ with $1/T$, and the slope and intercept gave respectively $\Delta H^{\pm}$ and $\Delta S^{\pm}$. For the trans and cis isomers, respectively, the enthalpies ($\Delta H^{\pm}$) were calculated to be 10.11 ± 0.7 kcal/mol and 9.20 ± 0.3 kcal/mol, and the entropies ($\Delta S^{\pm}$) were calculated to be −29.6 ± 2.4 eu and −40.3 ± 0.8 eu.

(15) For a review, see E. L. Eliel, *J. Chem. Educ.*, 126 (1960).

(16) (a) J. L. Mateos, C. Perez, and H. Kwart, *Chem. Commun.*, 125 (1967); (b) F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, **90**, 3251 (1968).

(17) R. Brettle, D. R. Brown, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 696 (1969).

(18) M. Shamma and J. B. Moss, *J. Amer. Chem. Soc.*, **83**, 5038 (1961).

(19) J. L. Imbach, A. R. Katritzky, and R. A. Kolinski, *J. Chem. Soc. B*, 556 (1966).

(20) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961.

Table I

Summary of Second-Order Rates of Methylation of *cis*- (I) and *trans*-4-*tert*-Butyl-*N*,*N*-dimethylcyclohexylamine (II) in Acetonitrile

	Temp, °K	k_2 (10^3 mol^{-1} sec^{-1})[a]	ln $K^{\pm}$	$\Delta G^{\pm}$, kcal/mol
Trans	273.6	23.7	−33.1209	18.009
	263.1	9.53	−33.9919	17.774
	245.1	2.38	−35.3078	17.199
Cis	296.1	1.61	−35.8863	21.117
	283.1	0.809*	−36.5315	20.553
	273.6	0.427*	−37.1382	20.193
	263.1	0.206*	−37.8271	19.779

[a] Obtained by dividing the average pseudo-first-order rate constants in Table II by the CH_3I concentration, which was 1.6 *M* or 0.80 *M* (*).

Table II

Pseudo-First-Order Rates of Methylation for *cis*- and *trans*-4-*tert*-Butyl-*N*,*N*-dimethylcyclohexylamines (I and II) in Acetonitrile

	Run no.	Temp, °C	k_1 (10^3 sec^{-1})	Av k_1 (10^3 sec^{-1})
Trans	1	0.5	39.3	
	2		34.5	
	3		39.8	
	4		38.0	37.9
	5	−10	16.4	
	6		15.2	
	7		15.5	
	8		14.0	15.2
	9	−28	4.63	
	10		3.88	
	11		3.62	
	12		3.11	3.81
Cis	13	23	2.58	
	14		2.54	
	15		2.63	2.58
	16	10	0.677	
	17		0.580	
	18		0.688	
	19		0.646	0.648
	20	0.5	0.324	
	21		0.352	
	22		0.358	
	23		0.331	0.341
	24	−10	0.163	
	25		0.167	0.165

Conclusions

It is found that the entropy of activation is more negative for the cis isomer than for the trans. This is what one would predict if the cis isomer is in the chair form, since the system becomes more congested and presumably more restricted in the transition state than does the trans isomer. On the other hand, if the cis isomer went over to a boat form in the transition state, since the entropy of a boat form is higher than that of a chair, other things being equal,[21] the entropy of activation should become more positive than that of the trans isomer, which it does not. There is no reason to think the cis isomer has a boat conformation in the starting material, and, in fact, there is good reason to think otherwise.[22] Compounds in which an axial *tert*-butyl would be required on a cyclohexane ring in a chair

(21) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **82**, 2393 (1960); N. L. Allinger and H. M. Blatter, *ibid.*, **83**, 994 (1961).

(22) Reference 9, p 216.

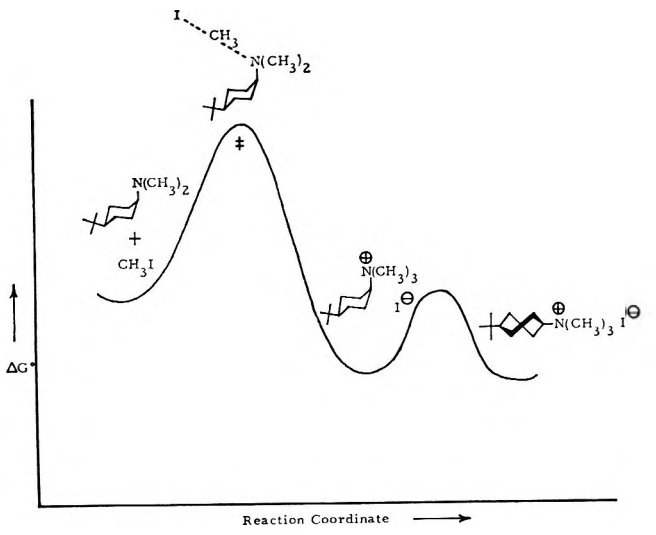


Figure 1.

form, such as *trans*-1,3-di-*tert*-butylcyclohexane, are found to have the ring largely in the boat conformation[21] and the methiodide of I should be also, although definite evidence on that point seems lacking.[23] The conclusions seem to be that the transition state is still chair, and near to starting material, and the reaction coordinate diagram must look approximately as summarized in Figure 1.

Experimental Section

cis-4-*tert*-Butylcyclohexanecarboxylic Acid.—This compound was prepared according to a known procedure.[24] Chromatography of the ethyl ester (8 ft, 15% SE-30 Chromosorb W at 175° and 60 cc/min.) showed the ester to be at least 98% cis.

cis-4-*tert*-Butylcyclohexylamine.—This compound was prepared from the acid according to the Schmidt method;[23] distillation yielded the amine, bp 91–92° (15 mm) [reported[23] 90° (15 mm)].

cis-4-*tert*-Butyl-*N*,*N*-dimethylcyclohexylamine (I).—This compound was prepared essentially according to the method of Curtin,[23,25] bp 105–106° (25 mm). Chromatographic analysis (*vide supra*, 145° and 100 cc/min.) showed the amine to be at least 97.5% cis and the remainder an impurity which was not the trans isomer. *Anal.* Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.75. Found: C, 78.58; H, 13.66.

trans-4-*tert*-Butylcyclohexanecarboxylic Acid.—The acid was prepared by known methods[11,23] and recrystallized from hexane, mp 172–174° (reported[24] 174–175°). Chromatography of the ethyl ester (*vide supra*) showed the acid to contain 98.4% of the trans isomer.

trans-4-*tert*-Butylcyclohexylamine.—This compound was prepared from the acid by the same method as used for the cis amine, bp 92–93° (17 mm).[23,26]

trans-4-*tert*-Butyl-*N*,*N*-dimethylcyclohexylamine (II).—This compound was prepared by a method identical with that used to prepare the cis amine I, bp 112–113° (28 mm). Chromatography (*vide supra*) showed that the amine was at least 99% trans. *Anal.* Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.75. Found: C, 78.86; H, 13.93.

Kinetic Measurements.—A solution of 100 mg ± 3.4 mg of amine was dissolved in 100 ml of acetonitrile (Matheson Coleman and Bell, AX 149, purified by distillation from magnesium sulfate under nitrogen) and stored under nitrogen. Resistance measurements were made on 10-ml aliquots of the standard amine solution to which was added 1.0 ml or 0.5 ml of methyl iodide (Matheson Coleman and Bell reagent grade IX 195) using an Industrial Instruments, Inc., conductivity bridge, Model No. RC16B2. The solution was kept under nitrogen during each kinetic run in a special cell designed to bubble nitrogen constantly through the solution.

Registry No.—I, 2523-69-5; II, 2523-68-4.

(23) D. Y. Curtin, R. D. Stolow, and W. Maya, *J. Amer. Chem. Soc.*, **81**, 3330 (1959), have interpreted the reactions of the methiodide of I in terms of a chair form, and it seems that there must be at least a substantial amount of chair in equilibrium with the boat.

(24) H. H. Lau and H. Hart, *ibid.*, **81**, 4897 (1959).

(25) S. H. Pine, *J. Chem. Educ.*, 118 (1968).

(26) A value of 142–145° (17 mm) has been reported by D. V. Nightingale, J. D. Kerr, J. A. Gallagher, and M. Maienthal, *J. Org. Chem.*, **17**, 1017 (1952), but it appears that this value is incorrect.

Crystalline Complexes of Macrocyclic Polyethers with Thiourea and Related Compounds

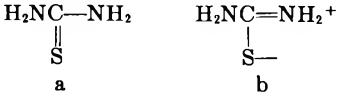
C. J. PEDERSEN

Contribution No. 215 from the Elastomer Chemicals Department, Experimental Station, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware 19898

Received December 11, 1970

Crystalline complexes of macrocyclic polyethers with thiourea and with compounds related to thiourea have been prepared. Their stoichiometry lies between one molecule of polyether to one to six molecules of the other component, but no obvious rule for fixing the ratios has been discovered. The sizes of the molecules and the stoichiometry appear to eliminate the possibility that these are inclusion compounds and the exact nature of these complexes has yet to be determined.

The preparation and properties of a number of macrocyclic polyethers derived from aromatic vicinal diols have been previously reported.[1] It was shown that dibenzo-18-crown-6,[2] one of the polyethers, forms complexes with ammonium and monosubstituted ammonium salts which contain separate anions. It was considered possible that thiourea (a) will assume the tautomeric



zwitterion form (b) and complex with the cyclic polyether. There also was the possibility, however remote, for the formation of inclusion compounds of cyclic polyethers and their salt complexes when they are exposed to thiourea under suitable conditions. If such inclusion compounds did form, they would be, in the case of the salt complexes, doubly wrapped salts, first surrounded by the polyether and then by thiourea. A short study, therefore, was undertaken to test these intriguing possibilities. When thiourea was actually found to form complexes with several macrocyclic polyethers, the action of some compounds related to thiourea was also investigated.

(1) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 7017 (1967).

(2) The abbreviated nomenclature for the cyclic polyethers is described in the first reference and will be used here without further explanation.

Results

In order to give greater significance to the melting points of the complexes, the melting points of the uncomplexed compounds are listed in Table I.

TABLE I
MELTING POINTS OF UNCOMPLEXED COMPOUNDS

Code no.	Compd	Mp, °C
XV	Dibenzo-14-crown-4	150–152
IV	Benzo-15-crown-5	79–79.5
XXV	Dibenzo-15-crown-5	113.5–115
XXI	Dibenzo-16-crown-5	117–118
X	Benzo-18-crown-6	43–44
XXVIII	Dibenzo-18-crown-6	164
XXIX	Bis(butylbenzo)-18-crown-6	135–137
LII	Benzocyclohexyl-18-crown-6	Below 26
XXXI	Dicyclohexyl-18-crown-6 (a mixture of two two-ring juncture isomers)	36–56
XXXIA	Pure isomer	61–62
XXXIB	Pure isomer	69–70
XXXV	Dibenzo-24-crown-8	113–114
S-1	Thiourea	180–182
S-2	*N*-Phenylthiourea	154
S-3	1-Phenylsemicarbazide	174–176
S-4	1-Phenylthiosemicarbazide	200–201
S-5	4-Phenylthiosemicarbazide	140
S-6	2-Thiazolidinethione	104–105
S-7	Thiobenzamide	115–116
	Sodium thiocyanate	287
	Potassium thiocyanate	173
	Potassium iodide	723
	Rubidium thiocyanate	188–190

The action of thiourea was determined simply by warming the polyethers with different proportions of a saturated (at 25°) methanol solution of thiourea, filtering the warm (40–50°) solution to remove undissolved polyether, and recovering any crystalline product that formed on cooling, taking care to minimize evaporation which would cause the thiourea to precipitate. The results obtained with several polyethers are shown in Table II. No other technique was used for the preparation of these products, and it is possible that other complexes could be formed under different conditions. Whether the composition of the complexes could be varied by precipitating the crystals at different fixed temperatures was not determined.

Thiourea did not form any complex with the following compounds: dibenzo-14-crown-4 (XV), 1,3-bis(*o*-methoxyphenoxy)propane (equivalent to an open XV), bis[2-(*o*-methoxyphenoxy)ethyl] ether (open XXV), and 1,14-dimethoxy-1,2,13,14-bis(tetramethylene)-3,6,-9,12-tetraoxatetradecane (open XXXI).

When thiourea was found to complex with several macrocyclic polyethers, some compounds related to thiourea were tested in connection with IV, XXVIII, and XXXI. The results obtained are shown in Table III. The proportions of reactants given in Table III were warmed in methanol and the mixtures treated as in the case of the thiourea complexes. Note that 4-phenylsemicarbazide which does not contain sulfur also forms a complex with XXXI. Dibenzo-18-crown-6 did not form an isolable complex with *N*-phenylurea and *N*-phenylthiourea, and no complex was formed between XXXI and the following compounds: Thiocarbanilide, *N*,*N*,*N*′-trimethylthiourea, tetramethylthiuram sulfide, tetraethylthiuram disulfide, 2-imidazolidinethione, and *N*-methyl-2-thiazolidinethione.

Finally, salt complexes of the polyethers or mixtures of salts and polyethers were treated with thiourea in methanol as described in detail in the Experimental Section. The results obtained are summarized in Table IV. Although some complexes of sodium and potassium salts add thiourea without decomposing, thiourea tends to displace ammonium, rubidium, and cesium from their complexes.

Discussion

The exact nature of the complexes of the macrocyclic polyethers with thiourea and related compounds is yet unknown. Their infrared spectra contain bands due to the components and appear to give little information on the probable mode of their interaction. The ultraviolet spectrum of the 1:1:1 complex of dibenzo-18-crown-6, potassium thiocyanate, and thiourea in methanol at a concentration which can be handled in a spectrophotometer is similar to that of the 1:1 complex of dibenzo-18-crown-6 and potassium thiocyanate, indicating that thiourea has no significant effect at very low concentrations. Higher concentrations of thiourea cannot be tested by this method because of interference in the region of 275 mμ.

They are not likely to be inclusion compounds of thiourea because the macrocyclic polyethers measure more than 6 × 7 Å in their smallest dimensions, the usual upper limit for the size of a guest molecule accommodated by thiourea.[3] Moreover, thiourea inclusion compounds usually consist of one molecule of guest compound and six or more molecules of thiourea.[4]

These complexes were then thought to be crystals with thiourea and related compounds present as interstitial components and that different numbers of molecules were required to fill the different vacancies in the crystals of the polyethers. This hypothesis seemed to be demolished when it was found that both urea and thiourea increase the solubility of dibenzo-18-crown-6 in methanol as shown in Table V.

Urea and thiourea both increase the solubility of dibenzo-18-crown-6 in methanol, suggesting that there is some interaction between them although the forces involved might have nothing to do with the presence of thiourea in the crystaline complexes. It is interesting that, in spite of the effect of urea shown in Table V, crystalline complexes of urea with the polyethers were not obtained when urea was handled in exactly the same way as thiourea. Possibly some other technique might have induced the formation of urea complexes.

Complexes such as $(XXXV)_2(thiourea)_7$ (Table II), $(XXVIII)_1(KCNS)_1(thiourea)_6$ (Table IV), and $(XXVIII)_1(RbCNS)_1(thiourea)_4$ (Table IV) have been included because the analytical results are reasonably good, and the melting point of the first is sharp although those of the others are not satisfactory. They may suggest that crystalline complexes of different thiourea content could be obtained by precipitating them from solutions of different compositions and at different temperatures.

(3) R. W. Schiessler and D. Flitter, *J. Amer. Chem. Soc.*, **74**, 1720 (1952).
(4) H. M. Powell, *J. Chem. Soc.* (*London*), 2658 (1954).

TABLE II

CRYSTALLINE COMPLEXES WITH THIOUREA

Reactants		Products					Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %	
Polyether	Ratio[a]	Yield,[b] %	Ratio[a]	Registry no.	Mp, °C	Formula	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
XV	15	No complex												
IV	5 to 7	74	4/1	28595-77-9	152–164	$C_{18}H_{36}N_8O_5S_4$	37.7	38.1	6.3	6.2	19.6	19.6	22.4	22.6
XXV	5 to 7	50	1/1	28595-78-0	115–117	$C_{19}H_{24}N_2O_5S$	58.2	58.5	6.1	6.0	7.1	7.0	8.2	8.4
XXI	5 to 7	93	1/3	28595-79-1	123–124	$C_{58}H_{70}N_2O_{15}S$	65.3	65.5	6.6	6.3	2.6	2.5	3.0	3.4
X	5 to 7	99	1/1	28595-80-4	127	$C_{17}H_{28}N_2O_6S$	52.6	53.3	7.2	7.3	7.2	7.6	8.3	9.5
XXVIII	12[c]	48	1/1	28595-81-5	165–166	$C_{21}H_{28}N_2O_6S$	57.8	57.7	6.4	6.4	6.4	6.3	7.3	7.6
XXIX			6/1	28595-82-6	178–180	$C_{34}H_{64}N_{12}O_6S_6$	44.0	43.1	6.9	7.0	18.1	18.1	20.7	20.5
LII	9 to 10	22[d]	6/1	28595-83-7	175–180	$C_{26}H_{54}N_{12}O_6S_6$	37.9	37.9	6.6	6.5	20.4	20.4	23.4	23.8
		36[e]	5/1	28595-84-8	167–174	$C_{25}H_{50}N_{10}O_6S_5$	40.2	41.5	6.7	6.6	18.8	17.7	21.5	21.7
XXXI[f]	9 to 10	66	6/1	28670-79-3	168–173	$C_{26}H_{60}N_{12}O_6S_6$	37.7	37.3	7.2	6.9	20.3	21.3	23.2	23.3
XXXI	5 to 7[g]	82	6/1		175–176	$C_{26}H_{60}N_{12}O_6S_6$	37.7	37.3	7.2	7.3	20.3	20.5	23.2	24.9
XXXI	2	21	6/1		189–193	$C_{26}H_{60}N_{12}O_6S_6$	37.7	38.7	7.2	7.1	20.3	20.3	23.2	27.1[h]
XXXIA	9 to 10	49	6/1		168–172	$C_{26}H_{60}N_{12}O_6S_6$	37.7	36.9	7.2	7.3	20.3	20.2	23.2	24.4
XXXIB	9 to 10	82	6/1		197–198	$C_{26}H_{60}N_{12}O_6S_6$	37.7	37.9	7.2	7.5	20.3	20.4	23.2	23.3
XXXV	5 to 7	78	7/2	28739-87-9	105–106	$C_{55}H_{92}N_{14}O_{16}S_7$	46.3	46.3	6.4	6.1	13.7	13.4	15.7	15.9

[a] Mole(s) of thiourea per mole(s) of polyether. [b] Yield based on polyether. [c] Twice the normal amount of methanol was used. [d] First crop. [e] Second crop. [f] XXXI was a mixture of two isomers. [g] Only 0.7 the normal amount of methanol was used. [h] No more sample for reanalysis.

TABLE III

CRYSTALLINE COMPLEXES WITH COMPOUNDS RELATED TO THIOUREA

Reactants			Products					Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %	
Polyether	Other	Ratio[a]	Yield,[b] %	Ratio[a]	Registry no.	Mp, °C	Formula	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
IV	S-7	2	68	2	28595-85-9	81–82	$C_{28}H_{34}N_2O_5S_2$	62.0	61.4	6.3	6.1	5.2	5.1	11.8	12.3
XXXI[c]	S-7	2	70	2	28595-86-0	154–156	$C_{34}H_{50}N_2O_6S_2$	63.2	63.1	7.7	7.3	4.3	4.5	9.9	10.0
XXXI	S-2	1	38	2	28595-87-1	179–180	$C_{34}H_{52}N_4O_6S_2$	60.3	60.0	7.7	7.6	8.3	8.3	9.5	9.8
XXXI	S-3	1	16	2	28670-80-6	150–158	$C_{34}H_{54}N_6O_8$	60.5	61.1	8.0	8.1	12.5	12.4		
XXXI	S-4	1	32	1	28595-88-2	155–165	$C_{27}H_{45}N_3O_6S$	60.1	60.3	8.4	8.4	7.8	7.9	5.9	6.0
XXXI	S-5	1	38	2	28595-89-3	144–145	$C_{34}H_{54}N_6O_6S_2$	57.8	57.9	7.6	7.8	11.9	11.8	9.1	8.8
XXXI	S-6	1	38	2	28595-90-6	125–127	$C_{26}H_{46}N_2O_6S_4$	51.2	51.1	7.5	7.4	4.6	4.7	21.0	21.3

[a] Mole(s) of additive per mole of polyether. [b] Yield based on polyether. [c] XXXI was a mixture of two isomers.

TABLE IV

CRYSTALLINE COMPLEXES WITH SALTS PLUS THIOUREA

Complex[a]	Yield,[b] %	Registry no.	Mp, °C	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %		Iodine, %	
					Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
$(IV)_2(KCNS)_1(S\text{-}1)_1$	36	28575-61-3	159–162	$C_{30}H_{44}N_8O_{10}S_7K$	50.8	50.8	6.2	6.1	5.9	6.2	9.0	9.6		
$(XXVIII)_1(NaCNS)_1\text{-}(S\text{-}1)_1$	38	28575-62-4	230–231	$C_{22}H_{28}N_3O_6S_2Na$	51.0	49.4	5.4	5.3	8.1	8.4	12.4	12.7		
$(XXVIII)_1(KCNS)_1\text{-}(S\text{-}1)_1$[c]	52	28575-63-5	242–253	$C_{22}H_{28}N_3O_6S_2K$	49.5	49.9	5.3	5.1	7.9	8.0	12.0	12.3		
$(XXVIII)_1(KCNS)_1\text{-}(S\text{-}1)_6$[d]	20	28575-64-6	164–183	$C_{27}H_{43}N_{13}O_6S_7K$	35.5	35.9	5.3	5.0	19.9	19.5	24.5	24.5		
$(XXVIII)_1(KI)_1(S\text{-}1)_1$	46	28575-65-7	208–210	$C_{21}H_{28}N_2O_6SIK$	41.8	42.0	4.7	4.5	4.7	4.9	5.3	5.8	21.1	19.7
$(XXVIII)_1(RbCNS)_1\text{-}(S\text{-}1)_4$	28	28575-66-8	160–190	$C_{26}H_{40}N_9O_6S_5Rb$	37.2	37.5	5.0	5.0	15.6	16.0	19.8	21.3		

[a] The preparation of these complexes is described in detail in the Experimental Section. [b] Yield based on polyether. [c] The first crop of crystals from a preparation. [d] The second crop of crystals from the same preparation.

TABLE V

EFFECTS OF UREA AND THIOUREA ON SOLUBILITY[a]

	Control	Urea	Thiourea
Undissolved polyether, g	2.651	2.330	2.156
Dissolved polyether, g	0.336	0.650	0.757
Dissolved polyether, mol	0.00093	0.0018	0.0021

[a] Polyether, 3 g of dibenzo-18-crown-6 (0.0083 mol); solvent, 100 ml of methanol; urea, 7.1 g (0.118 mol); thiourea, 9.0 g (0.118 mol); temperature, 59 ± 1°.

There appear to be certain inhibitions for the formation of the crystalline complexes; for example, if the polyether ring is too small (XV), no complex is formed, nor is one formed with open-chain equivalents of even the larger cyclic polyethers. Steric hindrance is also a factor since thiourea, *N*-phenylthiourea, and 2-thiasolidinethione form complexes but *N,N,N'*-trimethylurea, thiocarbanilide, and *N*-methyl-2-thiazolidinethione do not.

More work, probably in the field of single-crystal X-ray analysis, will be required for the elucidation of the structure of these crystalline complexes. Whatever forces are involved, they are not strong enough to displace a potassium ion from its complexes with 18-crown-6 polyethers.

Experimental Section

All inorganic compounds were reagent grade, and all solvents and available organic materials were commercial products used without purification. The macrocyclic polyethers were prepared according to published methods.[1]

The preparation of the thiourea complexes listed in Table II has been described in the text. The examples from Table III given below are typical for the preparation of these complexes.

Preparation of (Dicyclohexyl-18-crown-6)$_1$(2-thiazolidinethione)$_2$.—A mixture of 1.02 g (0.0086 mol) of 2-thiazolidinethione, 3.72 g (0.01 mol) of dicyclohexyl-18-crown-6, and 23 ml of methanol was heated, and the resulting clear solution was allowed to cool. The white crystals which formed were filtered, washed with methanol, dried, and weighed 2.0 g.

Preparation of (Dicyclohexyl-18-crown-6)$_1$(thiobenzamide)$_2$.—A mixture of 0.795 g (0.0058 mol) of thiobenzamide, 1.1 g (0.00296 mol) of dicyclohexyl-18-crown-6, and 10 ml of methanol was warmed, and the crystals which deposited were filtered, washed with methanol, and dried. The bright yellow crystals, 1.3 g, did not smell of thiobenzamide.

The preparations of the complexes given in Table IV are described below.

Preparation of (Benzo-15-crown-5)$_2$(potassium thiocyanate)$_1$(thiourea)$_1$.—A mixture of 10 ml of a saturated methanol solution of thiourea (0.97 g of thiourea, 0.013 mol) and 2 g (0.0032 mol) of (benzo-15-crown-5)$_2$(KCNS)$_1$ was warmed and the resulting clear solution was left at room temperature. The crystals which deposited within the solution in about 2 hr were filtered, washed with methanol, and dried. Colorless plates, 0.8 g, were obtained.

Preparation of (Dibenzo-18-crown-6)$_1$(sodium thiocyanate)$_1$(thiourea)$_1$.—A mixture of 15 ml of a saturated methanol solution of thiourea (1.46 g, 0.019 mol), 0.45 g (0.0056 mol) of sodium thiocyanate, 2 g (0.0056 mol) of dibenzo-18-crown-6, and 10 ml of methanol was warmed and the clear solution was concentrated to 15 ml. The white solid which deposited shortly (0.5 g) was found to be thiourea. More crystals which formed within the solution were recovered by decanting and drying on a porous plate. A white powder, 1.1 g, was obtained.

Preparation of (Dibenzo-18-crown-6)$_1$(potassium thiocyanate)$_1$(thiourea)$_1$.—A mixture of 15 ml of a saturated methanol solution of thiourea (1.46 g, 0.019 mol) and 2 g (0.0044 mol) of (dibenzo-18-crown-6)$_1$(KCNS)$_1$ was warmed, and the clear solution was decanted into another beaker and allowed to stand at room temperature. The mass of white crystals which formed within the solution was filtered, washed with cold methanol, and dried. A white solid, 1.2 g, was obtained. This is the first crop shown in Table IV.

More crystals were recovered from the filtrate. This white solid product is the second crop shown in Table IV. In spite of the acceptable analysis of this product as (dibenzo-18-crown-6)$_1$(KCNS)$_1$(thiourea)$_6$, its existence as a specific compound has yet to be proven.

Preparation of (Dibenzo-18-crown-6)$_1$(potassium iodide)$_1$(thiourea)$_1$.—A mixture of 50 ml of a saturated methanol solution of thiourea (4.85 g, 0.065 mol), 2.3 g (0.014 mol) of potassium iodide, and 5 g (0.014 mol) of dibenzo-18-crown-6 was warmed, and the clear solution was filtered and left at room temperature. Clusters of hard needles formed within the solution and they were filtered, washed with methanol, and dried (3.8 g).

When an identical reaction was run using an equivalent amount of ammonium iodide instead of potassium iodide, a 41% yield of (dibenzo-18-crown-6)$_1$(thiourea)$_1$ was obtained. Apparently, ammonium thiocyanate was expelled from the complex by the thiourea. (Dibenzo-18-crown-6)$_2$(CsCNS)$_1$ under similar conditions gave the same product, (dibenzo-18-crown-6)$_1$(thiourea)$_1$. Another experiment using strontium iodide instead of potassium iodide did not give any complex of definite composition.

Preparation of (Dibenzo-18-crown-6)$_1$(rubidium thiocyanate)$_1$(thiourea)$_4$.—A mixture of 15 ml of a saturated methanol solution of thiourea (1.46 g, 0.019 mol) and 2.2 g (0.0044 mol) of (dibenzo-18-crown-6)$_1$(RbCNS)$_1$ was warmed and the clear solution was allowed to stand at room temperature. Crystals did not form within the solution but on the walls of the beaker, both above and below the liquid level. All the crystals were scraped into the solution, broken up, filtered, washed with methanol, and dried (0.5 g). More crystals, 0.5 g, were obtained on allowing the filtrate to evaporate.

The composition of the products, (dibenzo-18-crown-6)$_1$(RbCNS)$_1$(thiourea)$_4$, corresponds closely to the mole ratio of the reactants. This suggests the possibility of a coprecipitate of the two reactants.

Attempted Preparation of (Dibenzo-18-crown-6)$_2$(CsCNS)$_1$(thiourea)$_n$.—On warming a mixture of 8 ml of a saturated methanol solution of thiourea (0.76 g, 0.01 mol) and 1 g (0.0011 mol) of (dibenzo-18-crown-6)$_2$(CsCNS)$_1$, a clear solution was obtained within which crystals began to form. The mixture was cooled in ice–water, filtered, washed with cold methanol, and dried. The white crystals, 0.5 g, were those of (dibenzo-18-crown-6)$_1$(thiourea)$_1$. Here again, the salt was displaced in the complex by thiourea.

Registry No.—Thiourea, 62-56-6.

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Notes

The Synthesis of *cis*- and *trans*-Tricyclo[6.4.0.0^{2,7}]dodeca-2,12-diene by the Intramolecular Coupling of Disilver Reagents[1a]

WILLIAM R. MOORE,* LAWRENCE N. BELL, AND GENE P. DAUMIT[1b]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Several simple alkenylsilver(I) compounds have been prepared and shown to undergo thermally induced decomposition to give conjugated dienes derived from coupling of the alkenyl groups. Thus vinylsilver affords 1,3-butadiene,[2a] 1-propenylsilver affords 2,4-hexadiene,[2b] and 2-butenylsilver affords 3,4-dimethyl-2,4-hexadiene.[2b] In the last two cases, the coupling was found to occur with retention of configuration indicating that free radicals were not involved. These reactions represent intermolecular coupling. It appeared to us that, if *intramolecular* coupling could be achieved, one would have a potentially useful way to effect unique ring closures. We have examined this possibility in a case of particular interest to us and have found that derivatives of 1,2-dimethylenecyclobutane can be prepared in good yield by intramolecular coupling of the appropriate disilver reagents.

Coupling of dibromide **1**[3] with magnesium affords a 1:1 mixture of *meso*- and *dl*-2,2′-dibromo-3,3′-bicyclohexenyl (**2**) from which the pure crystalline isomers can be obtained by fractional crystallization. The configurational assignments are based on the results reported below.

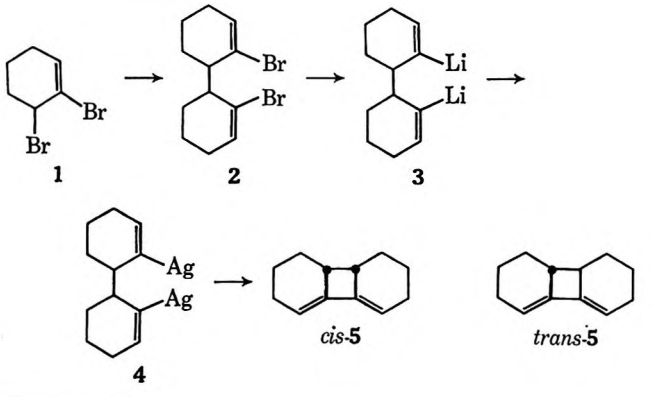
Treatment of either stereoisomer with excess *n*-butyllithium in ether at 25° gave the corresponding dilithium reagent **3**.[4] Reaction of the latter with anhydrous silver iodide at −78° gave the disilver reagent **4**, which upon warming to room temperature decomposed to give tricyclo[6.4.0.0^{2,7}]dodeca-2,12-diene (**5**) in *ca.* 70% yield (based on **3**). As was anticipated, stereochemistry was retained; *meso*-**2** gave only *cis*-**5** and *dl*-**2** gave only *trans*-**5**.

The structure of *trans*-**5** was established unequivocally by spectral and glc comparison with an authentic sample.[5] This structural assignment also establishes the configurational identity of the stereoisomers of **2** inasmuch as the coupling reaction, irrespective of mechanism, cannot affect the stereochemistry at the two centers in question (the 3,3′ positions of **2**).

The structure of *cis*-**5** is clearly confirmed by the mass, infrared, nmr, and ultraviolet spectra. The cis fusion can be deduced from the nmr spectrum since each of the tertiary allylic protons is deshielded by an adjacent trans C–C bond, causing a shift to δ 2.72, *ca.* 0.4 ppm downfield from the signal arising from the corresponding protons in *trans*-**5**.[6]

cis-Diene **5** is extremely reactive toward oxygen and it polymerizes readily when it is neat or in concentrated solutions. Examination of molecular models will show that *cis*-**5** must suffer substantial torsional strain which must be the cause of its high reactivity. Such strain is greatly diminished in *trans*-**5** by puckering of the four-membered ring.

The fact that dienes **5**, and the cis isomer in particular, can be obtained in good yield by this method[7] supports an absence[2b] of free radicals during the thermal decomposition of the disilver reagent since the high reactivity of *cis*-**5** clearly will make it serve as an efficient radical trap. The transition state for carbon–carbon bond formation thus must include at least one silver atom. Since coupling led to cyclization rather than polymerization, it appears likely that the carbon–carbon bond is formed between two ligands attached to a common silver atom. The disilver reagent formulated as **4** may in fact either be, or lead to, an "ate



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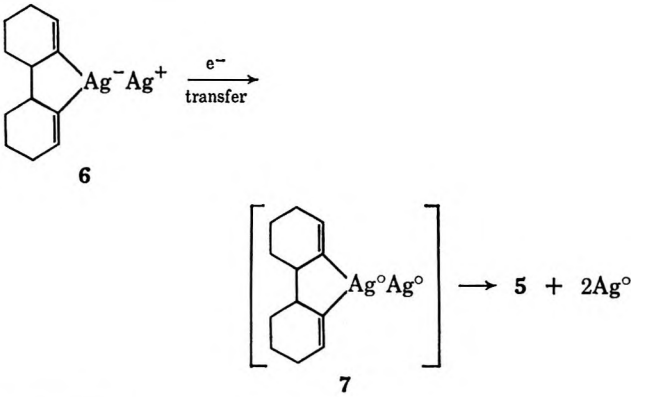

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(1) (a) Supported in part by the National Science Foundation (GP8181); (b) National Institutes of Health Predoctoral Fellow, 1967–1970.

(2) (a) A. K. Holliday and R. E. Pendlebury, *J. Organometal. Chem.*, **7**, 281 (1967); (b) G. M. Whitesides and C. P. Casey, *J. Amer. Chem. Soc.*, **88**, 4541 (1966).

(3) J. Sonnenberg and S. Winstein, *J. Org. Chem.*, **27**, 748 (1962).

(4) Dienes **5** were formed in very low yields in the preparation of **3**.

(5) W. R. Moore and W. R. Moser, *J. Amer. Chem. Soc.*, **92**, 5469 (1970).

(6) The signal for the tertiary allylic protons of *trans*-**5** is not resolved from the signals arising from other protons, but it cannot fall below *ca.* δ 2.3, where a shoulder appears on a broad band centered at *ca.* δ 2.2.

(7) The excess butyllithium employed to facilitate formation of **3** apparently does not interfere in subsequent steps probably because the butylsilver, which is formed, is decomposed before the decomposition of **4** starts.

complex"[8] such as 6. While 6 probably oversimplifies the total structure,[9] it represents the essential structural features. Based on the proposed intermediacy of 6, a rational reaction pathway can be envisioned. With both alkenyl moieties attached to the same silver atom, electron transfer from the anion to the cation, possibly producing an intermediate 7, should lead to a concerted breaking of the C–Ag bonds and forming of the C–C bond. Stretching of the C–Ag bonds in the sense of a homolytic cleavage must cause an overlap of the carbon orbitals resulting in bond formation.

Experimental Section[10]

2,3-Dibromocyclohexene (1).—6,6-Dibromobicyclo[3.1.0.]-hexane[3,5] (105 g, 0.44 mol) was added dropwise over 0.5 hr to a flask maintained at 155° to effect rearrangement to 1. Distillation afforded 95 g (90%) of 1, bp 70° (1.7 mm), n^{25}D 1.5761 (lit.[3] n^{25}D 1.5764).

2,2′-Dibromo-3,3′-bicyclohexenyl (2).—2,3-Dibromocyclohexene (95 g, 0.41 mol) was added rapidly to a suspension of 5.9 g (0.24 g-atom) of magnesium in 120 ml of refluxing ether. Refluxing was continued for 1 hr, water was added, and the ether layer was separated and dried (Na_2SO_4). Distillation afforded 35 g (57%) of 2, bp 135° (0.4 mm), n^{25}D 1.5780. Glc analysis (silicone nitrile XF-1150, 180°) indicated that the product was a 1:1 mixture of the *meso* and *dl* isomers. The ir and nmr spectra were superpositions of the spectra of the individual isomers reported below. The mass spectrum showed peaks at *m/e* 322, 320, and 318 in a 1:2:1 ratio (molecular ions of a dibromide).

Anal. Calcd for $C_{12}H_{16}Br_2$: C, 45.03; H, 5.04; Br, 49.92. Found: C, 44.87; H, 4.89; Br, 50.08.

The 1:1 mixture of *meso*- and *dl*-2 was found to crystallize from methanol to give lead fractions enriched in the less soluble *dl* isomer. Repeated fractional crystallization eventually produced pure samples of each isomer as shown by glc analysis. From *ca.* 30 g of the 1:1 mixture, 3–4 g of each pure isomer was obtained (prior to recycling).

meso-2: mp 54–55°; ir (CCl_4) 3035, 1635, and fingerprint bands (not in *dl*) at 1240, 1200, 1040, 1020, 965 (broad), 950, 915, 860 cm^{-1}; nmr (CCl_4) δ 1.75 (~8 H, m), 2.0 (~4 H, m), 2.84 (2 H, m), 6.13 (2 H, m).

dl-2: mp 67.5–69.5°; ir (CCl_4) 3035, 1640, and fingerprint bands (not in meso) at 1250, 1210, 1108, 1030, 980, 940, 922, 870 cm^{-1}; nmr (CCl_4) δ 1.72 (~8 H, m), 2.0 (~4 H, m), 3.02 (2 H, m), 6.15 (2 H, m).

***cis*-Tricyclo[6.4.0.0^{2,7}]dodeca-2,12-diene (*cis*-5).**—A solution of 12 ml of 1.6 *M* *n*-butyllithium in hexane and 1.51 g (4.7 mmol) of *meso*-2 in 45 ml of ether was stirred for 4 hr at room temperature. Analysis of an aliquot (the method is presented below) indicated a 65% yield of 2,2′-dilithio-3,3′-bicyclohexenyl (3). The dilithium reagent 3 was added to a suspension of 4.76 g (20 mmol) of anhydrous silver iodide in 40 ml of ether (to which 0.8 ml of 1.6 *M* *n*-butyllithium had been added to remove any traces of water) cooled to −78°. After being stirred for 25 min at −78°, the mixture was allowed to warm to room temperature. After 16 hr, the reaction mixture was filtered under nitrogen through Celite and the filtrate, diluted to 100 ml, was stored under nitrogen at −10°. In some instances, the reaction mixture was hydrolyzed and the ether layer was washed with water and dried (K_2CO_3) before storing. The yield of 5 was not changed.

Glc analysis (Carbowax 20M, 120–170°, using *n*-tridecane as in internal standard) established that *cis*-5 was formed in 70% yield based on the dilithium reagent (46% from 3). A small amount of 3,3′-bicyclohexenyl (2%) was found along with small amounts of several higher molecular weight materials which were not identified. Several repetitions of the reaction gave essentially the same overall yield of *cis*-5.

Pure *cis*-5 was obtained by preparative glc (Carbowax 20M, 150° and silicone SE 30, 90°) with the collected material being stored at liquid nitrogen temperatures prior to spectral and analytical measurements: ir (CCl_4) 3020, 2930, 2880, 2860, 2830, 1670, 1645 (w), 1450, 1435, 1335, 1250, 1205, 1135, 1065, 935, 875 cm^{-1}; nmr (CCl_4) δ 0.8–1.9 (complex m, 8 H), 2.1 (broad m, ~4 H, CH_2CH=C), 2.72 (broad m, 2 H, CH=CCH), 5.40 (m, 2 H, CH=C); mass spectrum *m/e* (relative intensity) 39 (28), 65 (21), 67 (21), 77 (32), 79 (44), 81 (22), 91 (91), 104 (37), 105 (30), 115 (25), 117 (90), 118 (27), 119 (31), 131 (59), 132 (37), 145 (65), 160 (100, M^+); uv (hexane) λ_{max} 256 [log ε 4.15 (5)], sh 246 and 265 nm.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.07. Found: C, 89.60; H, 10.20.

Attempts to obtain pure samples of *cis*-5 by distillation led to extensive polymerization with formation of a nonvolatile white solid. The pure liquid diene (from glc) was found to polymerize readily under helium at room temperature. It is extremely reactive toward oxygen; initial attempts to obtain a mass spectrum led to a peak at *m/e* 192 (*cis*-5 + O_2) and only a weak molecular ion peak at *m/e* 160.

Analysis of the dilithium reagent can be accomplished by quenching an aliquot with water and determining the yield of 3,3′-bicyclohexenyl by glc (Carbowax 20M, 120–170°) using *n*-tridecane as an internal standard. The amount of 3,3′-bicyclohexenyl formed in preparing the dilithium reagent, typically 2–3%, can be determined by quenching an aliquot with 1,2-dibromoethane followed by glc analysis. A small amount of methyllithium should be added to the dibromoethane immediately before use to ensure complete removal of traces of water or HBr. Very small amounts of 5 were formed during the preparation of 3; the maximum yields were in the range of 2–3%. This material presumably is derived from coupling of the 2-lithio-2′-bromo intermediate which is a precursor to 3.

***trans*-Tricyclo[6.4.0.0^{2,7}]dodeca-2,12-diene (*trans*-5).**—Using the same molar ratios of reactants employed in the preparation of *cis*-5, *dl*-2 was converted into *trans*-5 in overall yields of 41–45%. The product was identified by glc and infrared comparison with an authentic sample.[5]

The 1:1 mixture of *meso*- and *dl*-2 similarly gave a 1:1 mixture of *cis*- and *trans*-5 in essentially the same yields. On several glc columns employing different liquid phases (both polar and nonpolar), *cis*-5 was found to have a retention time *ca.* 10–20% longer than that of *trans*-5.

Registry No.—*meso*-2, 28229-12-1; *dl*-2, 28229-13-2; *cis*-5, 28229-14-3; *trans*-5, 28229-15-4.

(8) G. Wittig, *Quart. Rev., Chem. Soc.*, **20**, 191 (1966).

(9) The Ag^+ would probably be coordinated to the solvent and possibly halide ions and/or the ate complex 6 may be a part of a larger aggregate.

(10) Spectral measurements were determined with the following instruments: ir, Perkin-Elmer Model 237; nmr, Varian T-60; uv, Cary Model 14; mass spectra, Hitachi Perkin-Elmer RMU-6. Melting points are corrected and boiling points are not. All reactions were conducted under a nitrogen atmosphere.

A Convenient Synthesis of Alkyl-1,3,5-hexatrienes by Reaction of Dienyl Halides with 1,5-Diazabicyclo[4.3.0]non-5-ene[1]

C. W. SPANGLER,* R. EICHEN, K. SILVER, AND B. BUTZLAFF

The Michael Faraday Laboratories, Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115

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Most reported preparations of substituted 1,3,5-hexatrienes either yield mixtures or require several steps. The most common impurities from either acid-catalyzed or high temperature preparations are substituted 1,3-cyclohexadienes resulting from electrocyclic ring closure[2] and aromatics from dehydrogenation of the cyclic dienes.[3] Trienes free of these impurities may be obtained *via* a modified Hofmann elimination

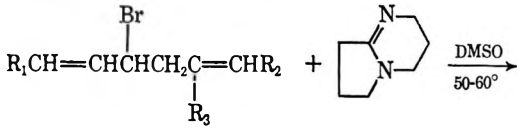
(1) Supported in part by a National Science Foundation Student Science Training Program Grant, GW-5221.

(2) C. W. Spangler and N. Johnson, *J. Org. Chem.*, **34**, 1444 (1969).

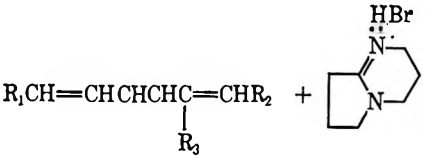
(3) C. W. Spangler, *ibid.*, **31**, 346 (1966).

sequence which we have described previously.[4,5] We would now like to report a new preparation of acyclic trienes of high purity (99%) in yields comparable to the Hofmann sequence.

1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)[6] has recently been shown to be a highly versatile dehydrohalogenation reagent reactive under much milder conditions than with most other basic reagents.[7,8] In fact, dehydrohalogenation can be realized between 25 and 80° in dimethyl sulfoxide (DMSO). Volatile products can then be distilled directly from the reaction media.



1, $R_1 = R_2 = R_3 = H$
2, $R_1 = R_3 = H; R_2 = CH_3$
3, $R_1 = R_3 = CH_3; R_2 = H$



The observed ease of reaction and isolation is in marked contrast to other common means of dehydrohalogenation. For example, 1,3,5-hexatriene can be obtained from 3-bromo-1,5-hexadiene in 30% yield with DBN–DMSO, while potassium *tert*-butoxide–DMSO yields only polymeric material under identical conditions.

Both the Hofmann and DBN syntheses of pure trienes utilize common dienyl bromide intermediates, obtained from appropriately substituted hexadienols by treatment with phosphorus tribromide, without further purification.[9] However, it then becomes necessary in the Hofmann sequence to prepare an appropriate quaternary ammonium salt by treatment of the bromide with a tertiary amine such as *N*,*N*-dimethylbenzylamine. In most reported examples, in particular those from primary or secondary allylic bromides, this "salt" is precipitated as an impure glass whose further purification, prior to decomposition in base, is quite difficult.[4,5] Direct dehydrohalogenation with DBN, however, eliminates these difficulties.

As examples of the synthetic utility of the DBN–DMSO procedure, the following trienes were prepared: 1,3,5-hexatriene (**1**), 1,3,5-heptatriene (**2**), and 2-methyl-1,3,5-heptatriene (**3**). The results are shown in Table I and compared to reported Hofmann results. An interesting result is the difference in the trans/cis ratio for the two procedures. For **1** and **2**, this difference (approximately a factor of two) indicates that the DBN reaction probably is of the Saytzeff type. However, other workers have reported that base-catalyzed isomerizations producing substituted trienes show a marked preference for trans orientation.[10] Similarly, Bartsch[11] has recently shown that base-induced eliminations in DMSO under conditions of negligible product isomerization show unusually high trans/cis ratios. However, these correlations cannot explain the presence of *cis*-2-methyl-1,3,5-heptatriene in the DBN–DMSO product and its absence in the Hofmann product. The reason for this difference remains obscure.

TABLE I

Triene	% yield[a] DBN–DMSO	% yield[a] Hofmann	*trans*-Triene/*cis*-triene[b] DBN–DMSO	*trans*-Triene/*cis*-triene[b] Hofmann
1	30	59[c]	5.0	2.3[c]
2	39	35[d]	2.7	1.3[d]
3	26	10	5.6	*e*

[a] Overall yield based on substituted hexadienol. [b] Isomer ratio of incipient double bond. [c] See ref 13. [d] See ref 5. [e] Only the trans,trans isomer was obtained.

Experimental Section[12]

DBN Dehydrohalogenation. General Procedure.—The substituted bromohexadiene (*ca.* 0.50 mol) is dissolved in 40 cc of DMSO[12b] and added to a solution of DBN (0.55 mol) in 50 cc of DMSO dropwise, with stirring, so as to maintain the reaction temperature between 50 and 60°. During the course of the reaction the medium quickly turns from colorless to a deep golden yellow. After the addition is complete, the product is distilled at reduced pressure (20–100 mm) and collected in an ice-cooled flask.

1,3,5-Hexatriene (**1**).—1,5-Hexadien-3-ol (0.55 mol) was allowed to react with phosphorus tribromide (0.23 mol) essentially by the method of Hwa, *et al.*,[13] yielding 75 g of crude bromodiene, a mixture of allylic isomers. The bromohexadiene (75 g, 0.475 mol) was then treated as described above in the general procedure with DBN (65 g, 0.525 mol). The product **1** was obtained as a colorless liquid (11.3 g, 30%): $n^{25}D$ 1.5106; bp 78–80°; uv max 265, 255, 245 nm (ϵ 4.12, 4.97, 3.44 × 10^4); nmr τ 4.6–5.1 (m, 4 H, CH_2=), 3.35–4.0 (m, 4 H, CH=CH) [lit.[13] bp 80°; $n^{25}D$ 1.5091; uv max 265, 255, 245 nm (ϵ 4.40, 5.30, 3.60 × 10^4) for trans isomer]. Glpc analysis revealed a purity of 98.9% and an isomer distribution of 83.5% trans and 16.5% cis.

1,3,5-Heptatriene (**2**).—1,5-Heptadien-4-ol (91 g, 0.76 mol) was allowed to react[5] with 90 g (0.33 mol) of phosphorus tribromide yielding 127 g of the crude bromodiene. The crude bromide was then allowed to react with DBN (96 g, 0.77 mol) as described above yielding **2** (27.6 g, 39%): bp 28–30° (20 mm); $n^{26}D$ 1.5253; uv max 270, 260, 250 nm (ϵ 3.80, 4.55, 3.33 × 10^4); nmr τ 8.25 (d, 3, J = 6 Hz, =CCH_3), 3.0–5.1 (m, 7 vinyl hydrogens) [lit.[5] bp 30–32° (25 mm); $n^{24}D$ 1.5239; uv max 270, 260, 250 nm (ϵ 3.56, 4.45, 3.33 × 10^4)]. Glpc analysis revealed a purity of 99.2% and an isomer distribution of 73.0% trans and 27.0% cis.

2-Methyl-1,3,5-heptatriene (**3**). A.—*trans*-2-Methyl-1,5-heptadien-4-ol[15] (100 g, 0.79 mol) was allowed to react with phosphorus tribromide (90 g, 0.33 mol) yielding 121 g of crude bromide. Half of the bromohexadiene (60.5 g, 0.32 mol) was allowed to react with DBN (46 g, 0.37 mol) as described above yielding **3** (9.0 g, 26%): bp 68–70° (25 mm); $n^{25}D$ 1.5263; uv max 272, 262, 252 nm (ϵ 3.84, 4.68, 3.48 × 10^4); nmr τ 8.0–8.3 (m, 6, $2CH_3C$=), 5.05 (s, 2, CH_2=), 3.6–4.6 (m, 4, CH=CH) [lit.[14]

(4) C. W. Spangler and G. F. Woods, *J. Org. Chem.*, **28**, 2245 (1963).
(5) C. W. Spangler and G. F. Woods, *ibid.*, **30**, 2218 (1965).
(6) Aldrich Chemical Co., Inc., Milwaukee, Wis.
(7) K. Eiter, *Justus Liebigs Ann. Chem.*, **682**, 62 (1965).
(8) H. Oediger, H. Kabbe, F. Moller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).
(9) The present authors recognize, as have previous workers, that the crude dienyl bromides are mixtures of allylic isomers.
(10) E. A. Zuech, D. L. Crain, and R. F. Kleinschmidt, *J. Org. Chem.*, **33**, 771 (1968).
(11) R. A. Bartsch, *ibid.*, **35**, 1334 (1970).
(12) (a) Gas–liquid partition chromatography was performed with an Aerograph Model 202-1B dual column instrument equipped with a Hewlett-Packard Model 3370 electronic integrator for peak area measurement; dual 15-ft 15% TCEP on 60–80 mesh Chromosorb W columns were used for all separations. Ultraviolet spectra were obtained in isooctane with a Cary Model 14 spectrophotometer, and nmr spectra were obtaind with a Varian A60-A using TMS as an internal standard ($CDCl_3$ solvent). All spectra were consistent with the assigned structures, and satisfactory C and H analyses were obtained for all compounds. Identification of geometric isomers was accomplished by direct comparison (gc retention times and peak enhancement by admixture, and uv spectra) with known samples (see ref 2, 13, and 14) prepared in our laboratory. (b) DMSO was J. T. Baker reagent grade, used without further purification.
(13) J. C. H. Hwa, P. L. deBenneville, and H. J. Sims, *J. Amer. Chem. Soc.*, **82**, 2537 (1960).
(14) T. S. Sorensen, *Can. J. Chem.*, **42**, 2781 (1964).
(15) Chemical Samples Co., Columbus, Ohio.

n^{25}D 1.5232; uv max 274, 263.5, 253,5 nm (trans,trans isomer) (ϵ 3.56, 4.48, 3.18 × 10^4); nmr (CCl_4) identical with that above but shifted due to solvent difference]. Glpc analysis revealed a purity of 99.0% and an isomer distribution of 84.8% trans,trans and 15.2% cis,trans.

B.—Half of the above crude bromide (60.5 g, 0.32 mol) was allowed to react with *N*,*N*-dimethylbenzylamine (61 g, 0.45 mol) in 500 ml of toluene at 50–60° for 24 hr. After cooling, the toluene was decanted from the brown glassy salt which was then dissolved in *ca.* 500 ml of water. The resulting yellow solution was added dropwise to a KOH solution (70 g/1200 ml of water) undergoing distillation. The product was worked up in the usual manner[4,5] and distilled yielding **3** (3.5 g, 10%). Glpc analysis revealed a purity of 99% but essentially only one isomer, *trans,trans*-**3** with only a trace of the *cis,trans*-**3**.

Registry No.—*trans*-**1**, 821-07-8; *cis*-**1**, 2612-46-6; **2**, 2196-23-8; *trans,trans*-**3**, 17679-94-6; *cis,trans*-**3**, 18304-16-0; DBN, 3001-72-7.

Cyclobutene Epoxides. The Stereospecific Lewis Acid Rearrangement[1]

DAVID L. GARIN

Department of Chemistry, University of Missouri—St. Louis, St. Louis, Missouri 63121

Received September 9, 1970

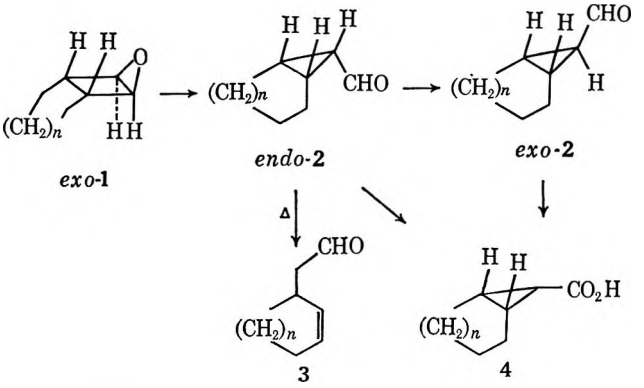
Despite numerous reports on the Lewis acid rearrangement of cyclobutene epoxides to cyclopropyl carbonyl compounds, the possible stereospecificity of the reaction (by analogy to other cycloalkene epoxides) has not been reported.[2-5]

Our investigation was prompted by the fact that the determination of the stereospecificity would enhance the synthetic utility of the reaction and by the availability of two cyclobutene epoxides suitable for such a study, bicyclo[3.2.0]hept-6-ene oxide (**1**, n = 1) and bicyclo[4.2.0]oct-7-ene oxide (**1**, n = 2).[6]

Results

The epoxides were prepared by the peracid oxidation of the corresponding cyclobutenes giving the exo isomer of **1** (n = 1)[7] and the exo and endo isomers of **1** (n = 2) which were separable by gas chromatography.[8]

Treatment of the exo isomers of **1** (n = 1, 2) with concentrated solutions of anhydrous lithium iodide in ether in a stoppered flask at *ca.* 40° for 1–24 hr produces a rearrangement to the exo and endo isomers of the ring-contracted bicyclic carboxaldehydes **2** (n = 1, 2) in varying amounts. Prolonged reaction time favors the formation of the exo isomer. Product mixtures were analyzed by vpc although the *endo*-carboxaldehydes **2** (n = 1, 2) rearrange on the vpc column to the corresponding Δ^2-cycloalkenyl acetaldehydes **3** (n = 1, 2) under the conditions employed.[9] The *exo*-carboxaldehydes **2** (n = 1, 2) were separated and collected by preparative vpc. Silver oxide oxidation under nonisomerizing conditions gives the known *exo*-carboxylic acids **4** (n = 1, 2).[10,11]



Our results suggested an initial isomerization of the *exo*-epoxides (**1**) to the bicyclic *endo*-carboxaldehydes (**2**) followed by a slower but competitive epimerization of *endo*-**2** to *exo*-**2**. This was verified by utilizing proton nmr spectroscopy to follow the rearrangement. Lithium iodide was added to an nmr sample of *exo*-**1** (n = 2) in $CDCl_3$ at room temperature. After 1 hr, the epoxide proton absorption had decreased and an aldehydic signal at 9.6 ppm had appeared in the spectrum (see Table I). After 4 hr, with 20% of **1** still unreacted, a new aldehyde signal at 9.1 ppm began to appear in the spectrum. After 16 hr, we obtained a ratio of 1:1 for the signals at 9.6 and 9.1 ppm assigned to the endo and exo isomers of **2** (n = 2), respectively. These two products can account for all of the absorptions observed in the spectrum[12] which is in perfect agreement with those of the known compounds.[9]

TABLE I

REARRANGEMENT OF *exo*-**1** (n = 1, 2) WITH LITHIUM IODIDE IN $CDCl_3$[a]

Time, hr	% of compound[b]					
	exo-1		*endo*-2		*exo*-2	
	n = 2	n = 1	n = 2	n = 1	n = 2	n = 1
0	100		0		0	
1	65		35		0	
2	40		60		0	
3	25		75		0	
4	20		80		Trace	
16	0	90	50	10	50	
23	0	85	30	15	70	
43	0	80	10	20	90	
64	0	70	0	25	100	5

[a] These data were obtained using 55 mg of *exo*-**1** (n = 1, 2) and 60 mg of lithium iodide in 0.4 ml of $CDCl_3$. [b] Based on integration of epoxide proton *vs.* aldehydic proton absorptions.

A similar experiment utilizing *exo*-**1** (n = 1) produced a slower conversion of epoxide to carboxaldehyde (Table I). Molar amounts of lithium iodide are not essential but lesser amounts reduce the rates of the reactions.

(1) Abstracts, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, ORGN 137.
(2) J. L. Ripoll and J. M. Conia, *Tetrahedron Lett.*, 979 (1965).
(3) J. L. Ripoll and J. M. Conia, *Bull. Soc. Chim. Fr.*, 2755 (1965).
(4) W. R. Moore and C. H. Beede, Abstracts, 144th National Meeting of the American Chemical Society, Los Angles, Calif, 1963, 11M.
(5) An extensive review of epoxide chemistry can be found: A. Rosowsky, "Heterocyclic Compounds with Three- and Four-Membered Rings," part 1, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, pp 1–523.
(6) D. L. Garin, *J. Org. Chem.*, **34**, 2355 (1969).
(7) L. A. Paquette, A. A. Youssef, and M. L. Wise, *J. Amer. Chem. Soc.*, **89**, 5246 (1967).
(8) A. C. Cope and R. W. Gleason, *ibid.*, **84**, 1928 (1962).
(9) D. L. Garin, *J. Org. Chem.*, **35**, 2830 (1970).
(10) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Amer. Chem. Soc.*, **85**, 582 (1963).
(11) J. A. Berson and E. S. Hand, *ibid.*, **86**, 1978 (1964).
(12) The solid lithium iodide contained ether whose proton absorptions served as an internal standard for integrations.

The *endo*-carboxaldehydes **2** do not epimerize in ether or $CDCl_3$ in the absence of lithium iodide. The nature and extent of this surprisingly facile epimerization is currently under investigation.

In an attempt to avoid the epimerization of the *endo*-carboxaldehydes during the rearrangement of the *exo*-epoxides, another Lewis acid was employed. The reaction of *exo*-**1** (n = 2) with a molar excess of lithium thiocyanate in ether gave *endo*-**2** (n = 2) with no formation of *exo*-**2**. The exo isomer of **1** (n = 1) was stable to prolonged treatment with lithium thiocyanate in ether at 40°.

As expected, *endo*-**1** (n = 2) reacts with lithium iodide to give *exo*-**2** (n = 2). Thus, these Lewis acid rearrangements of cyclobutene epoxides to cyclopropyl carboxaldehydes occur with net retention of configuration at the migration terminus.

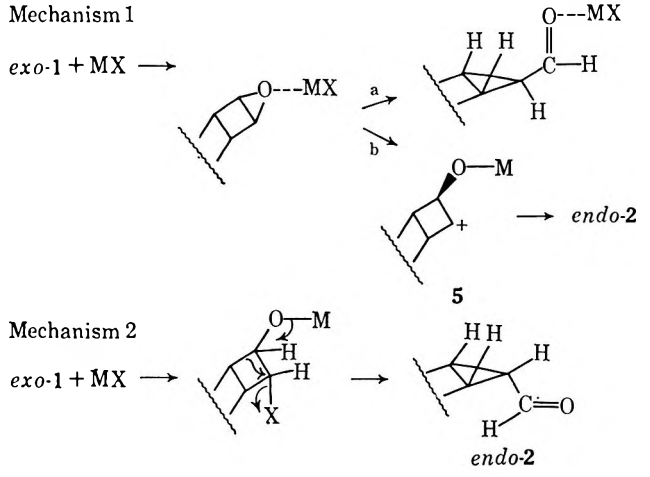
Discussion

At least two possible mechanisms must be considered for the rearrangement. The formation of a Lewis acid–epoxide complex would result in polarization of the C–O bond with subsequent rearrangement to the cyclopropyl carbonyl compound possibly through a cyclobutyl carbonium ion intermediate (mechanism 1). A concerted, unimolecular process (path a) would be expected to occur with inversion.[13,14] A nonconcerted two-step process (path b) would lead to a cyclobutyl carbonium ion. If this is indeed an intermediate, the rearrangement would have to be governed by the stereochemistry of the C–O linkage of **5** since exo and endo species lead to different products, an unlikely possibility.[14] Moreover, the cyclobutyl carbonium ion would be expected to rearrange to olefinic products.[15]

Alternatively, the Lewis acid could add across the epoxide bond to give the lithio salt of the *trans*-iodohydrin followed by rearrangement with alkyl displacement of iodine (mechanism 2). Both steps would be expected to occur with inversion of configuration resulting in net retention. Treatment of α-chlorocyclobutanols with base resulted in the formation of cyclopropyl carboxaldehydes with alkyl displacement of chlorine occurring with inversion of configuration.[16] The addition of lithium iodide to cyclohexene oxide is reported to give the *trans*-iodohydrin lithio salt (isolated as the iodohydrin). Subsequent base treatment of *trans*-cyclohexane iodohydrin resulted in the formation of the ring-contracted cyclopentane carboxaldehyde among other products.[17,17a]

Our attempts to isolate a cyclobutane iodohydrin were unsuccessful. No absorptions attributable to the lithio salts of these compounds were observed in the nmr spectra while the reactions were occurring but high concentrations of these reactive intermediates would not be expected (the reaction of α-chlorocyclobutanols with lithium *tert*-butoxide in chloroform produces the cyclopropyl carboxaldehydes in minutes).[18]

The latter mechanism, which we favor, can account for the discriminatory reactivity of lithium thiocyanate toward **1** as well as the difference in the rates of rearrangement with lithium iodide. Back-side displacement of the large anions on the exo isomer of **1** (n = 1) would be more difficult than that of **1** (n = 2) due to the greater rigidity of the fused five-membered ring of the former.



Experimental Section[19]

exo- and *endo*-**1** (n = 2).—The mixture of isomers was synthesized as reported.[6] Separation of isomers was effected on a 20 ft × 3/8 in. Carbowax 20M column (30% of 45–60 Chromosorb W) at 190° with carrier flow *ca.* 85 ml/min. Compounds isolated and retention times in minutes were *endo*-**1** (n = 2), 27; *exo*-**1** (n = 2), 34; unknown, 31. Approximate ratios of *endo*-**1**:*exo*-**1**:unknown were 2:15:1 from integration of peak areas on the chromatogram.

Rearrangement and Epimerization Reactions of 1 in Ether. Reactions with Lithium Iodide.—To 24 mg (18 mmol) of anhydrous lithium iodide[20] in 1.0 ml of anhydrous ether in a 5-ml round-bottom flask was added 155 mg (120 mmol) of *exo*-**1** (n = 2). The flask was stoppered and immersed in an oil bath at 42° and the solution was stirred *via* a magnetic bar for 20 hr. After cooling, the crude reaction mixture was poured onto a 6-in. column of silica gel and eluted with benzene. After collection of 200 ml of benzene, the solvent was removed by rotary evaporator giving 152 mg of product. $CDCl_3$ was immediately added and the nmr spectrum taken. Integration of peaks at 9.6, 9.1, and 3.5 ppm showed a ratio of *endo*-**2**:*exo*-**2**:*exo*-**1** (n = 2) of 75:15:10. The $CDCl_3$ was removed by a rotary evaporator and the residue added to 240 mg of anhydrous lithium iodide (180 mmol) in 1.0 ml of anhydrous ether in a 5-ml round-bottom flask. The flask was stoppered tightly and placed in an oil bath at 40° for 14 hr with stirring. Similar work-up gave 140 mg of product whose nmr spectrum was now superimposable with that of the known *exo*-**2** (n = 2).[9]

In a similar fashion, the reaction of 195 mg of *exo*-**1** (n = 1) with 262 mg of lithium iodide in 1.0 ml of anhydrous ether at 42° for 48 hr produced *endo*-**2**:*exo*-**2**:*exo*-**1** (n = 1) in the ratio of 25:70:5 as determined by nmr analysis (peaks at 9.5, 9.1, and 3.5 ppm, respectively) in collaboration with peak integration of chromatograms and comparison with the known compounds.[9]

The reaction of 43 mg of *endo*-**1** (n = 2) with 63 mg of lithium iodide in 1.0 ml of anhydrous ether at 38° for 16 hr produced 40 mg of a product which was identical with *exo*-**2** (n = 2).

Heating *exo*-**1** (n = 1, 2) and *endo*-**2** (n = 1,2) in ether at 40° for 36 hr in the absence of lithium iodide followed by the normal work-up gave no rearrangement products.

Reactions with Lithium Thiocyanate.—To 153 mg of lithium thiocyanate in 1.0 ml of anhydrous ether was added 166 mg of

(13) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).

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(15) K. B. Wilberg and J. G. Pfeiffer, *J. Amer. Chem. Soc.*, **92**, 553 (1970).

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(18) D. L. Garin, unreported results.

(19) All melting points are uncorrected. All nmr spectra were taken in $CDCl_3$ on a Perkin-Elmer R-20 60-Mc instrument utilizing TMS as internal standard. An Aerograph Model A-700 vpc was used extensively.

(20) M. D. Taylor and L. R. Grant, *J. Amer. Chem. Soc.*, **77**, 1507 (1955).

exo-1 (n = 2). The flask was stoppered and stirred at 41° for 34 hr. Work-up as described above gave 150 mg of a product whose nmr spectrum was consistant with that of known *endo*-2 (n = 2) and displayed no *exo*-2 aldehydic signal at 9.1 ppm.[9] Air oxidation of the carboxaldehyde gave an acid identical with authentic bicyclo[4.1.0]heptane-7-*endo*-carboxylic acid (4, n = 2).[11]

The reaction of 30 mg of *exo*-1 (n = 1) with 11 mg of lithium thiocyanate in 0.5 ml of ether at 40° for 48 hr resulted in the recovery of starting material.

Rearrangement and Epimerization Reactions of 1 in $CDCl_3$.—Samples of the epoxides 1 were dissolved in 0.4 ml of $CDCl_3$ and the nmr spectrum was recorded. Solid lithium iodide was then added to the nmr tube which was shaken briefly (the lithium iodide is only partially soluble in $CDCl_3$) and the spectrum was recorded immediately. The lithium iodide contained ether[21] (*ca.* 20% by weight) whose proton absorptions were utilized as an internal standard. Periodic scans showed changes in absorption for the epoxide and aldehydic protons (see Table I). Integration of the peaks in these regions relative to one another allowed a determination of the progress of the reaction, and integration relative to the ether proton signals substantiated the proton count. Data for the individual reactions of 55 mg of *exo*-1 (n = 1) and 55 mg of *exo*-1 (n = 2), both with 60 mg of lithium iodide, are listed in Table I.

A similar experiment with 53 mg of *endo*-1 (n = 2) and 30 mg of lithium iodide produced a 90:10 product mixture of *exo*-2:-*endo*-1 (n = 2) after 14 hr as determined by nmr and vpc analyses. The rates of the above reactions in $CDCl_3$ are extremely slow when the molar ratio of lithium iodide to epoxide is less than 1:5.

Silver Oxide Oxidation of *exo*-2.—Following reported procedures,[10] 60 mg of *exo*-2 (n = 2) in 0.5 ml of ethanol and 0.60 g of silver nitrate in 1.0 ml of water were placed in a 10-ml round-bottom flask. To this was added dropwise with stirring a solution of 0.20 g of sodium hydroxide in 2.0 ml of water. After being stirred for 1 hr, the reaction mixture was filtered and the filtrate acidified with 3 N HCl. The white solid was filtered (46.4 mg) and the aqueous solution extracted with ether to yield, after evaporation, another 15.0 mg of solid. Recrystallization from hexane gave crystals which had mp 95–96° (reported[11] for bicyclo[4.1.0]heptane-7-*exo*-carboxylic acid, mp 95–96.5°).

Identical fashion, *exo*-2 (n = 1) gives a white solid acid, mp 58° (reported[10] for bicyclo[3.1.0]hexane-6-*exo*-carboxylic acid, mp 58°).

Registry No.—*exo*-1 (n = 1), 18684-66-7; *exo*-1 (n = 2), 28541-57-3; *endo*-1 (n = 2), 28541-58-4.

Acknowledgment.—The author is grateful to the Petroleum Research Fund (1207-G1) and the Research Committee, UMSL, for financial support.

(21) The ether is not essential. Similar results are obtained with commercial anhydrous lithium iodide (Alfa Inorganics, Beverly, Mass.).

The Synthesis and Diels–Alder Reactivity of 2-Ferrocenylbutadiene[1a]

RONALD W. NOVAK,*[1b] TRAVIS E. STEVENS, AND MORRIS HOWARD

Rohm and Haas Company, Redstone Research Laboratories, Huntsville, Alabama 35807

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We wish to report on the synthesis and characterization of 2-ferrocenybutadiene and some of its Diels–Alder adducts. The synthetic approach taken to the title compound was through dehydration of 2-hydroxy-2-ferrocenylbutene. The latter compound may be obtained in good yield from reaction of the readily available acetylferrocene and vinylmagnesium bromide. The dehydration of the alcohol is a delicate procedure because of the acid and heat sensitivity of the diene product; a variety of acid-catalyzed routes to 2-ferrocenylbutadiene were attempted without success. The method of choice is reaction with methyl chloroformate in the presence of pyridine. The intermediate carbonate decomposes under the reaction conditions to give the desired product.

The current interest in α-ferrocenylcarbonium ions[2] coupled with the possible zwitterionic character of the Diels–Alder reaction[3] prompted a study of the Diels–Alder activity of 2-ferrocenylbutadiene. Dienophiles such as maleic anhydride, *p*-benzoquinone, nitrosobenzene, and acryloylferrocene were found to add readily to form 1:1 adducts. The characterization of these compounds is given in Table I. No attempts were made to isolate minor products. Attempted reactions with dimethyl maleate and with cyclohexene were unsuccessful. The former compound appeared to catalyze decomposition of the diene to unidentified products.

TABLE I
PROPERTIES OF THE DIELS–ALDER ADDUCTS OF 2-FERROCENYLBUTADIENE[a]

Dienophile[d]	Adduct mp, °C	Adduct nmr, δ
Maleic anhydride (12504-80-2)	147	5.95 (s, 1, vinyl), 4.26 (m, 4, ferrocenyl), 4.11 (s, 5, ferrocenyl), 3.40 (m, 2, methine), 2.55 (m, 4, methylene)
p-Benzoquinone (12504-81-3)	137–138	6.69 (s, 2, vinyl), 5.83 (m, 1, vinyl), 4.20 (m, 9, ferrocenyl), 3.30 (m, 2, methine), 2.60 (m, 4, methylene)
Nitrosobenzene[b] (12504-82-4)	86–87	7.22 (m, 5, phenyl), 5.92 (m, 1, vinyl), 4.48 (m, 2, methylene), 4.36 (m, 2, ferrocenyl), 4.21 (m, 2, ferrocenyl), 4.11 (s overlapping m, 7, ferrocenyl and methylene)
Acryloylferrocene[c] (12504-89-1)	161–162	5.96 (m, 1, vinyl), 4.82 (m, 2, ferrocenyl), 4.51 (m, 2, ferrocenyl), 4.33 (m, 2, ferrocenyl), 4.21 (s, ferrocenyl), 4.10 (s, ferrocenyl); total area 4.21 + 4.10 = 12

[a] Satisfactory analysis for C, H, and Fe were obtained for the adducts in this table. The data were made available to the referees and to the editor. [b] The expected product is 2-phenyl-5-ferrocenyl-3,6-dihydro-1,2-oxazine. See ref 2. [c] The expected product is 1-ferrocenyl-4-ferrocenoylcyclohexene-1. See ref 3d. [d] Registry numbers appear in parentheses.

It is concluded that 2-ferrocenylbutadiene is an active diene with a variety of dienophiles. More detailed studies are necessary to adequately weigh the electronic and steric effects of the 2-ferrocenyl group.

(1) (a) This work was sponsored by the U. S. Army Missile Command, Redstone Arsenal, Ala., under Contract DAAHO1-70-C-0146. (b) Rohm and Haas Co., Spring House, Pa. 19477.

(2) See J. Feinburg and M. Rosenblum, *J. Amer. Chem. Soc.*, **91**, 4324 (1969), and references cited therein.

(3) For recent discussions on the mechanism of the Diels–Alder reaction, see (a) S. Seltzer, *Advan. Alicycl. Chem.*, **2**, 1 (1968); (b) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970; (c) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967); (d) J. A. Titov, *Russ. Chem. Rev.*, 267 (1962).

Experimental Section

The melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Unless noted all nmr spectra were obtained on a Varian A-60 spectrometer, with deuteriochloroform as solvent and tetramethylsilane as the internal standard.

Preparation of 2-Hydroxy-2-ferrocenylbutene.—A 2.13 *M* vinylmagnesium bromide solution in tetrahydrofuran (12 ml) was added over a 20-min period to a solution of 5.0 g of acetylferrocene[4] in 40 ml of dry tetrahydrofuran. The solution was refluxed for 2 hr and then allowed to cool to room temperature. A solution of aqueous ammonia saturated with ammonium chloride was added until a solid precipitated from solution. The mixture was filtered, and the residue was washed with ether and combined with the filtrate. The combined ether solution was washed with water until neutral and dried ($MgSO_4$), and the solvent removed under reduced pressure to leave a deep red oil. This material was stored at 0° and used without purification. The yield was 5.2 g (93%); ir (CCl_4) 3400, 3100, 1635, 1100, 998, and 815 cm^{-1}; nmr (CCl_4) 6.15 (m, 2, vinyl), 4.10 (m, 9, ferrocenyl), 2.62 (s, 1, hydroxyl), 1.48 (s, 3, methyl).

Preparation of 2-Ferrocenylbutadiene.—To a solution of 15.0 g (59 mmol) of 2-hydroxy-2-ferrocenylbutene and 11.5 g (145 mmol) of pyridine in 300 ml of dry benzene, a solution of 12.3 g (130 mmol) of methyl chloroformate in 50 ml of benzene was added over a 1-hr period. The temperature was controlled at 5° during the addition. After the addition was complete, the solution was allowed to warm to ambient temperature and the stirring continued until gas evolution ceased (about 16 hr). The reaction solution was washed three times with 250-ml portions of water and dried ($MgSO_4$), and the solvent removed under reduced pressure without heating. The resulting oil was extracted with 500 ml of pentane. Methylene chloride (16 ml) was added to the pentane solution, and the resulting solution passed through a silica gel (100–200 mesh) column cooled to 5°. The 2-ferrocenylbutadiene is the only component of the reaction solution which passed through the column under these conditions. After solvent removal at low temperature, 5.6 g (40%) of a deep red, heavy oil is obtained: ir (CCl_4) 3110, 1650, 1585, 1105, 1000, 918, and 818 cm^{-1}; nmr ($CDCl_3$) 7.0–5.0 (m, 5, vinyl), 4.35 (m, 2, ferrocenyl), 4.22 (m, 2, ferrocenyl), 4.10 (s, 5, ferrocenyl).

Anal. Calcd for $C_{14}H_{14}Fe$: C, 70.62; H, 5.93; Fe, 23.46. Found: C, 70.96; H, 6.03; Fe, 23.80.

This compound was stored at 0° as a 25% solution in benzene.

Preparation of Acryloylferrocene.—β-Dimethylaminopropionylferrocene hydrochloride was prepared by the method of Hauser, Pruett, and Mashburn[5] from acetylferrocene, formaldehyde, and dimethylamine hydrochloride. The hydrochloride salt was dissolved in water and neutralized with sodium hydroxide, and the free amine extracted into ether. Methyl iodide (1 equiv) was added to the ether solution and the mixture allowed to stand for 12 hr. The resulting quaternary ammonium salt was then filtered from the ether and suspended in a two-phase solution of methylene chloride and sodium hydroxide–water. The sodium hydroxide was in fivefold excess. The three-phase system was stirred until the solid disappeared and a deep red color developed. The organic layer was then separated and dried ($MgSO_4$), and the solvent removed under reduced pressure leaving a red oil which can be crystallized from ethanol–water. (It was sometimes necessary to chromatograph the oil through silica gel before recrystallization.) Yields varied from 30 to 70%. The product melted at 72.5–73° (lit.[5] 73.5–74°).

General Procedure for the Preparation of the Diels–Alder Adducts.—The dienophile (1 equiv) was added to a 25% solution of 2-ferroeenylbutadiene in benzene. The reaction solution was stirred at ambient temperature until the diene ir peaks at 918 and 880 cm^{-1} vanished (15 min–20 hr). In the case of maleic anhydride, the product precipitated from the reaction mixture after 15 min. With acryloylferrocene and *p*-benzoquinone, the products precipitated when the reaction solution was poured into a 20-fold excess of pentane. With nitrosobenzene, the solvent was stripped from the reaction mixture and the resulting oil passed through a silica gel (100–200 mesh) column. The product was eluted with a pentane–methylene chloride ratio of 5:1. All the adducts were recrystallized from hot ethanol.

Registry No.—2-Ferrocenylbutadiene, 12-504-78-8; 2-hydroxy-2-ferrocenylbutene, 12504-79-9.

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The Formation of Sulfur–Selenium and Selenium–Selenium Bonds by Chloramination

HARRY H. SISLER* AND NIRMAL K. KOTIA

Department of Chemistry, University of Florida, Gainesville, Florida 32601

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The various reactions of chloramines R_2NCl (R = alkyl or H) with amines, phosphines, arsines, and stibines have been extensively investigated in this laboratory.[1-10] Sisler, *et al.*,[11] have recently shown that chloramines bring about the oxidative coupling of thiols to yield disulfides, RSSR. We were interested in determining whether similar chloramination reactions with selenols or mixtures of thiols and selenols would yield RSeSeR′ or RS–SeR′ compounds (R or R′ is an aryl or alkyl group and R and R′ may be identical or different).

There are numerous references[12-18] to the preparation of diselenides by methods other than chloramination. Likewise, the formation of compounds containing sulfur–selenium bonds by methods[16,19,20] other than chloramination have been reported.

We have, therefore, studied the reactions of chloramine and of dimethylchloramine with several selenols and with mixtures of thiols and selenols and have found that these reactions provide methods for the synthesis of diselenides and selenosulfides which are more convenient than previously described methods and which, in a number of instances, give a purer product in higher yields.

Experimental Section

Materials.—Selenophenol, thiophenol, and 1-butanethiol were obtained from Eastman Organic Chemicals. Magnesium turnings, selenium powder, and *n*-butyl bromide were obtained from Fischer Scientific Co., and 2-naphthalenethiol was obtained from J. T. Baker Chemical Co. The purities of the thiols and selenols

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TABLE I
RESULTS OF CHLORAMINATION REACTIONS

Reactants A	Reactants B	Reactants C[c]	Mole ratio (reactants) A:B:C or A:C	Products[a]	Mole ratio (products)	Bp (mm) or mp, °C	Yield[b] %
C_6H_5SeH		$(CH_3)_2NCl$	1.50:1.00	$C_6H_5SeSeC_6H_5$[d]		59–61[e]	87
C_6H_5SeH		$NH_3 + NH_2Cl$	1.78:1.00	$C_6H_5SeSeC_6H_5$		59–60[e]	88
n-C_4H_9SeH		$(CH_3)_2NCl$	1.48:1.00	$C_4H_9SeSeC_4H_9$		106–7(4)[f]	89
n-C_4H_9SeH		$NH_3 + NH_2Cl$	1.64:1.00	$C_4H_9SeSeC_4H_9$		114–15 (8–9)	86
C_6H_5SH	C_6H_5SeH	$(CH_3)_2NCl$	1.00:1.00:1.07	$C_6H_5SSeC_6H_5$[g,h]		57–58[e]	85
C_6H_5SH	C_6H_5SeH	$NH_3 + NH_2Cl$	1.00:1.00:1.08	$C_6H_5SSeC_6H_5$[i,h]		57–58[e]	88
n-C_4H_9SH	n-C_4H_9SeH	$(CH_3)_2NCl$	1.00:1.00:1.10	$C_4H_9SSC_4H_9$		91–92 (5.5)	
				$C_4H_9SeC_4H_9$	5.6:1.0:2.2	104–6 (5.5)	83
				$C_4H_9SeSeC_4H_9$		110–13 (5.5)	
n-C_4H_9SeH	C_6H_5SeH	$(CH_3)_2NCl$	1.00:1.00:1.14	$C_4H_9SeC_6H_5$		85–87 (2)	
				$C_4H_9SeSeC_4H_9$	1.0:1.8:2.6	93–95 (2)	81
				$C_6H_5SeSeC_6H_5$[j]		135–37 (0.5–0.6)	
n-C_4H_9SH	C_6H_5SeH	$(CH_3)_2NCl$	1.00:1.00:1.06	$C_4H_9SSC_4H_9$		69–71 (1.25)	
				$C_6H_5SeSeC_6H_5$[j]	4.0:3.5:1.0[k]	152–55 (0.8)	61
				$(C_4H_9)_2S_2SeC_6H_5$ (?)[l]		92–94 (1.0)[l]	
β-$C_{10}H_7SH$	C_6H_5SeH	$(CH_3)_2NCl$	1.00:1.00:1.06	$C_6H_5SeSeC_6H_5$	1.29:1.00	57–58	89
				β-$C_{10}H_7SS$-β-$C_{10}H_7$[m]		136–38	

[a] Ammonium chloride or dimethylammonium chloride was formed from chloramine and dimethylchloramine, respectively, in almost quantitative yields. [b] Based on selenol and thiol taken. In cases of mixtures of two selenols and/or thiols, the overall yield is reported. [c] C added dropwise to A or to an equimolecular mixture of A and B. [d] Shining yellow crystals from hot absolute alcohol. [e] Turns deep red when heated gradually above the melting point, but returns to original yellow color on gradual cooling. [f] Light yellow liquid, offensive odor. [g] *Anal.* Calcd for $C_{12}H_{10}SSe$: C, 54.3; H, 3.7; Se, 29.7. Found: C, 53.8; H, 3.9; Se, 29.7. [h] Brilliant yellow needles recrystallized from hot methanol. [i] *Anal.* Calcd for $C_{12}H_{10}SSe$: C, 54.3; H, 3.7. Found: C, 53.4; H, 3.7. The ir spectrum for it agrees with the product referred to by footnote *g*. [j] Solidifies in condenser; hot water condenser used. [k] Appreciable quantity of black material, presumably selenium, was left in distilling flask. [l] Orange-red liquid, wt = 1.7 g (Bu_2S_2 = 3.7 g, Ph_2Se_2 = 5.65 g); ^1H nmr spectrum shows phenyl, methylene, and methyl protons (ratio of phenyl protons to methylene and methyl protons = 5:18). *Anal.* Found: C, 49.70; H, 6.88; S, 19.16; Se, 23.65. Mol wt (by vapor press osmometer) 293.7 suggests empirical formula $C_{14}H_{23}S_2Se$. The vpc shows a single broad peak only. All data available suggests two butyl and one phenyl group and two sulfur and one selenium atom in the compound. It was not further characterized ($n^{22}D$ 1.4326; d^{25}_4 1.1230). [m] Partly insoluble in ether, separated from dimethylammonium chloride using benzene in which only the disulfide is soluble. More disulfide obtained by fractional crystallization of ethereal solution. $n^{20}D$'s for Bu_2Se, $PhSeBu$, Bu_2Se_2, Bu_2S_2, and Ph_2Se are respectively 1.4748, 1.5684, 1.5402, 1.4908, and 1.6476. d^{25}_4's for Bu_2Se, $PhSeBu$, Bu_2Se_2, Bu_2S_2 are respectively, 1.1432, 1.2210, 1.3982, and 0.921.

were checked by comparison of indices of refraction[21] and densities[21] ($n^{20}D$, respectively, for PhSeH, BuSeH, BuSH, and PhSH of 1.6142, 1.4740, 1.4416, 1.5788; and d^{25}_4, respectively, for PhSeH, BuSeH, BuSH, and PhSH of 1.4856, 1.2344, 0.8428, and 1.5860), infrared spectra,[22,23] and melting or boiling points[21] with the corresponding data in the literature. All solvents used were of reagent grade and were purified by appropriate means and stored over calcium hydride, except for absolute ethanol, which was used as received.

1-Butaneselenol was prepared[24] by the reaction of selenium with butylmagnesium bromide,[25] followed by treatment with gaseous hydrogen chloride. This selenol, a light yellow liquid, distils between 113 and 115°. The commonly poor yields of this selenol are presumably a result of the rapid oxidation of this compound to the corresponding diselenide.

Analyses.—The Galbraith Microanalytical Laboratory, Knoxville, Tenn., conducted the elemental analyses. Molecular weights were determined by vapor pressure osmometer (Model 320, Mechrobal Inc.). Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Beckman Model IR-10 grating infrared spectrophotometer. ^1H nmr spectra were recorded with a Varian A-60 spectrometer.

All the sulfides, selenides, or selenosulfides prepared show bands in the region 300–700 cm^{-1} of the infrared spectrum. However, the infrared spectra are of limited use in these compounds, since only small differences in frequencies are found for the C–S, C–Se, S–S, S–Se, and Se–Se stretchings in the 300–700-cm^{-1} region. Moreover, the bands are frequently weak or poorly defined.

Synthesis of Chloramines.—Anhydrous chloramine was prepared by the method of Sisler and Mattair[26] which involves the gas-phase chlorination of ammonia. Ethereal solutions of chloramine were prepared by the procedure of Sisler and Gilson[27] and stored over calcium hydride at 0–5°. Dimethylchloramine was prepared by a procedure analogous to the Raschig synthesis of chloramine.[28] It was dissolved in diethyl ether and stored over calcium chloride.

General Procedure for Chloramination Reactions.—All manipulations were performed in an efficient hood or in an all-glass vacuum line. Chloramine and dimethylchloramine concentrations in reacting solutions were estimated iodometrically. An ethereal solution of chloramine or dimethylchloramine was added dropwise to a solution of the selenol (or a mixture of selenols or a mixture of a selenol and a thiol) in dry diethyl ether with constant stirring. The reactions were carried out at 25°, unless stated otherwise. Air and moisture were excluded. The reaction mixture soon became warm, dense white fumes were evolved, and a white precipitate formed immediately. In the initial stages, color changes of the reaction mixture from light yellow to orange-red were observed. The reaction mixture was stirred overnight, and was then refluxed for periods of from 1 to 2 hr. Ammonium chloride or dimethylammonium chloride, as the case may be, was removed by filtration. All the diselenides or selenosulfides reported herein are soluble in ether, except di-β-naphthyl disulfide. Ether and excess of chloramine were removed by reducing the pressure and trapping them in Dry Ice–acetone cooled traps. The products obtained were characterized by melting or boiling points,[29] infrared and proton magnetic resonance spectra, analytical data, and molecular weights. All analyses, unless otherwise noted, had percentages of C and H and molecular weights within 0.5% of the calculated values. The indices of refraction and densities (Table I) agree with reported literature values.[30,31] In cases of mixtures of compounds, fractional crys-

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tallization or distillation was employed to separate the components, as shown in the Table I. The solids were recrystallized from appropriate solvents.

Reaction of 2-Sulfenamidopyridine with 2-Mercaptopyridine.—2-Sulfenamidopyridine (mp 79–80°) was prepared by the method of Hurley and Robinson[32] involving the reaction of an aqueous solution of chloramine with an aqueous solution of the sodium salt of 2-mercaptopyridine. 2-Sulfenamidopyridine was dissolved in diethyl ether and an equivalent amount of 2-mercaptopyridine (mp 127–28°) in diethyl ether was added to it dropwise at 0–5°. When the reaction mixture was allowed to stand for 2 hr and the ether evaporated, 2,2′-dipyridyl disulfide (mp 51–52°) was obtained in almost quantitative yields.

Results and Discussion

The synthesis of Se–Se and S–Se bonded compounds by the chloramination of corresponding selenols or mixtures of selenols and thiols is recommended because of its simplicity and the fact that the diselenide or selenosulfide is easily obtained in high purity and good yield.

The monoselenides reported in Table I might have been formed from the diselenides with the elimination of selenium ($R_1R_2Se_2 \rightarrow R_1R_2Se + Se$).

The exclusive formation of diphenyl selenosulfide from the chloramination of a mixture of thiophenol and selenophenol may reasonably be attributed to reactions of selenenyl halide (formed as an intermediate) and thiophenol or sulfenyl halide and selenophenol.

$$C_6H_5SCl + C_6H_5SeH \longrightarrow C_6H_5SSeC_6H_5 + HCl$$
$$C_6H_5SeCl + C_6H_5SH \longrightarrow C_6H_5SSeC_6H_5 + HCl$$

A possible alternative explanation[33] is that one of the reactants (*e.g.*, R′SH) may react with one of the symmetrical diselenides to produce the unsymmetrical compound RSSeR′. Since exchange is possible,[34,35] the distribution of diselenide and disulfide may have resulted in part from such disproportionation reactions as follow.

$$RSSR + R'SeSeR' \rightleftharpoons 2RSSeR'$$
$$RSSR + R'SeH \rightleftharpoons RSSeR' + RSH$$
$$RSeSeR + R'SH \rightleftharpoons RSSeR' + RSeH$$

However, the mild conditions of the reactions make such exchanges improbable.

It was observed that at room temperature the liquid diselenides are, in general, bright orange in color, but this coloration becomes less intense as the temperature is lowered. This suggests partial dissociation into RSe radicals, which increases with rising temperature. However, in our present investigations free radical mechanisms are improbable since the reactions have been studied in ether and at low temperature (25° or lower). Furthermore, it has been shown that the reactions proceed almost instantaneously even in the dark and there seems to be no induction period. This rules out the free radical mechanism for the formation of disulfides, diselenides, and selenosulfides.

Diselenides resemble the disulfides in their chemical properties. Thus, there is no cleavage of the Se–Se bond when diphenyl diselenide or di-*n*-butyl diselenide is treated with chloramine or dimethylchloramine in ether under various sets of experimental conditions (temperatures varying between 0 and 25°, reaction times up to 72 hr, and a variety of ratios of concentrations of reactants). The diselenide was almost quantitatively recovered in all such experiments. It was reported earlier[11] that sulfur–sulfur bonds are not cleaved by the action of chloramines on disulfides. This suggests that the formation of disulfide or diselenide is not the first step in the chloramination of thiols and selenols. Otherwise it is difficult to explain the formation of both sulfenamide and disulfide[11] by the action of chloramine on thiols in other media.

A possible mechanism may be the formation of the sulfenamide or selenenamide as the first step in the reaction equation

$$RXH + NR_2'Cl \xrightarrow[R' = H, CH_3]{X = S, Se} RXNR_2' + HCl$$

followed by the reaction with an additional molecule of RXH to form diselenide, disulfide, or selenosulfide.

$$RXH + RXNR_2' \xrightarrow[= \text{same or different}]{R \text{ and } X} RXXR + R_2'NH$$

The reaction of 2-sulfenamidopyridine with 2-pyridinethiol resulting in the formation of 2,2′-dipyridyl disulfide and also the reported formation of sulfenamides by reactions of aqueous solutions of chloramine over aqueous alkali mercaptides[32,36–38] support the above mechanism. Also reactions of sulfenamides resulting in the formation of disulfides have been reported in the literature.[36,38,39]

It is assumed in this mechanism that the reaction of the sulfenamide or selenenamide with thiol or selenol to form disulfide, diselenide, or selenosulfide is relatively fast in comparison with the reaction of chloramine with thiol or selenol to form sulfenamide or selenenamide.

The additional possibility of formation of compounds of the type RSCl or RSeCl as intermediates may also be considered.[36,40] This would be in accord with the the colors observed (from light yellow to orange-red) during the course of the reaction.[17,19] It is possible that the sulfenamide or selenenamide formed from the chloramination of selenol and thiol may be cleaved by hydrogen chloride[41,42] to give the corresponding sulfenyl or selenenyl chlorides. In this case, the sulfenyl or selenenyl chlorides so formed could react spontaneously with the thiols or selenols to give the disulfides, diselenides, or selenosulfides.[43–45]

Registry No.—$C_6H_5SeSeC_6H_5$, 1666-13-3; $C_4H_9SeSeC_4H_9$, 20333-40-8; $C_6H_5SSeC_6H_5$, 28622-58-4; C_4H_9-

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SSC_4H_9, 629-45-8; $C_4H_9SeC_4H_9$, 14835-66-6; $C_4H_9SeC_6H_5$, 28622-61-9; β-$C_{10}H_7SS$-β-$C_{10}H_7$, 5586-15-2.

Acknowledgment.—We gratefully acknowledge the support of this research by the National Science Foundation through Research Project GP-4505 with the University of Florida.

A Mechanistic Study of 1,2-Glycol Cleavage with Nickel Peroxide

RYUSEI KONAKA*[1] AND KAZUO KURUMA

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

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It has previously been found by Nakagawa, Igano, and Sugita[2] that nickel peroxide[3] is a useful oxidant for the oxidative cleavage of 1,2-diols and related compounds, as are periodic acid, lead tetraacetate, phenyliodoso acetate, and sodium bismuthate. In connection with mechanistic studies[4] on nickel peroxide oxidations reported recently, which explained the oxidative action of nickel peroxide in terms of its having characteristic abilities for both hydrogen abstraction and OH radical donation, we have investigated the mechanism of the unusual oxidative cleavage of 1,2-diols with nickel peroxide.

The fact that the oxidation of *meso*-hydrobenzoin with nickel peroxide (50°, 1 hr) gives benzaldehyde in 85% yield, while that of pinacol (70°, 3 hr) gives acetone in 61% yield[2] indicates that elimination of the hydrogen on the α position of the 1,2-glycol is not necessary in the oxidative cleavage of 1,2-diols with nickel peroxide. In order to establish this, the isotope effects in the oxidative cleavage of *meso*-1,2-diphenyl-1,2-dideuterioethane-1,2-diol and *meso*-2,3-dideuteriobutane-2,3-diol were examined, since the oxidation of a monohydric alcohol with nickel peroxide begins with hydrogen abstraction at the α position of the alcohol (k_H/k_D = 7.4 on the oxidation of benzhydrol).[4] The values of the pseudo-first-order reaction rate constants determined by a thermoanalytical technique[5] are shown in Table I. The data suggest that no isotope effect occurs in either reaction within the experimental error.

For comparison of this reaction with a typical radical reaction of 1,2-glycols, azoisobutyronitrile was allowed to react with *meso*-hydrobenzoin to give benzil exclusively. Furthermore, investigation of the product distribution in the oxidation of *meso*-hydrobenzoin and *meso*-1,2-diphenyl-1,2-dideuterioethane-1,2-diol with nickel peroxide in order to reveal the difference between the radical oxidation and the oxidative cleavage with nickel peroxide was carried out to obtain the results as listed in Table II. Benzil did not react at all with nickel peroxide at 30°. This means that benzaldehyde is not afforded from benzil with nickel peroxide. The fact[3] that benzoin reacts with nickel peroxide to give a 98% yield of benzil suggests that the production of benzil from *meso*-hydrobenzoin with nickel peroxide would be attributable to the abstraction of α hydrogen of the glycol, which is the ordinary radical oxidation type, to yield benzoin followed by the oxidation of it. The substitution of deuterium for α hydrogen would make slowly the abstraction reaction at the α position to yield benzil.

For clarification of the characteristic of the reaction of 1,2-glycols with nickel peroxide, the relative oxidation rates of *meso*-hydrobenzoin, benzhydrol, and benzylphenylcarbinol are shown in Table I. The results suggest that substitution of the α-hydroxybenzyl group for the benzyl group increases the reactivity to nickel peroxide by about 800 times.

Subsequently, it could be assumed that the oxidative cleavage of 1,2-glycols with nickel peroxide takes place by way of a cyclic complex in a similar manner to that with lead tetraacetate and periodic acid.[6] However, if this were the case, a sharp distinction between the cis and trans glycols would be expected. Table III, where the reaction rates of the oxidation of *cis*- and *trans*-cyclopentane-1,2-diol with nickel peroxide are compared, shows that the behavior of 1,2-glycols with nickel peroxide, which is a one-electron oxidant type, is remarkably different from that with lead tetraacetate, the valence of which is immediately reduced

TABLE I

RATE CONSTANTS FOR THE OXIDATION OF 1,2-GLYCOLS AND RELATED COMPOUNDS WITH NICKEL PEROXIDE

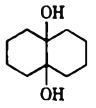
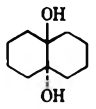
Substrate	Registry no.	Temp, °C	k, sec^{-1}
$(C_6H_5C(OH)H-)_2$	579-43-1	31	4×10^{-2}
$(C_6H_5C(OH)D-)_2$	28795-90-6	31	5×10^{-2}
$(CH_3C(OH)H-)_2$	5341-95-7	1	6.8×10^{-4}
$(CH_3C(OH)D-)_2$	28795-91-7	1	9.1×10^{-4}
$C_6H_5CH_2CH(OH)C_6H_5$	614-29-9	30	5.2×10^{-5}
$C_6H_5CH(OH)C_6H_5$	91-01-0	30	5.3×10^{-4}
$C_6H_5CH(OH)CH(CH_3)C_6H_5$	28795-94-0	30	1.5×10^{-5}
	28795-95-1	1	4.7×10^{-6}
		20	No reaction

TABLE II

PRODUCT DISTRIBUTION ON THE OXIDATION OF *meso*-HYDROBENZOIN AND *meso*-1,2-DIPHENYL-1,2-DIDEUTERIOETHANE-1,2-DIOL WITH NICKEL PEROXIDE[a]

Compd	Temp, °C	Products, % yield— Benzaldehyde	Benzil
$(C_6H_5C(OH)H-)_2$	30	84.4	8.1
	1	71.2	31.8
	−11[b]	21.9	53.1
$(C_6H_5C(OH)D-)_2$	30	100	0
	−11[b]	45.3	Trace

[a] In benzene. [b] Unchanged 1,2-glycols were recovered.

(1) Author to whom correspondence should be addressed.

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TABLE III

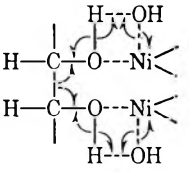
COMPARISON OF THE REACTION RATE OF THE OXIDATION OF *cis*- AND *trans*-CYCLOPENTANE-1,2-DIOL

Cyclopentane-1,2-diol	Rate ratio— Nickel peroxide k (sec^{-1}), 1°	Lead tetraacetate[a] k (mol^{-1} l. min^{-1}), 20°
cis-	3.56×10^{-3}	40,000
trans-	1.69×10^{-3}	12.8
k_{cis}/k_{trans}	2.1	3,120

[a] R. Criegee, E. Büchner, and W. Walther, *Chem. Ber.*, **73**, 571 (1940).

by two units as pointed out by Heidt, Gladding, and Purves.[7]

Therefore, it is not unreasonable to propose that the oxidative cleavage of 1,2-glycols takes place by a concerted mechanism through the formation of a noncyclic nickel complex as shown tentatively below.



The result that the reaction rate of 1,2-diphenylpropyl alcohol with nickel peroxide was slow compared with *meso*-hydrobenzoin (Table I) suggests that the stepwise or concerted cleavage mechanism started from only one reaction site would not be probable, since the methyl group may stabilize the cleaved radical in a similar manner as the hydroxyl group.[8] Furthermore, the reaction of decahydronaphthalene-*trans*-9,10-diol with nickel peroxide did not occur at all at 20°, while that of the cis isomer proceeded even at 1° though it was not fast compared with *cis*- and *trans*-cyclopentane-1,2-diol (Table I and III). This means that both hydroxyl groups of decahydronaphthalene-*trans*-9,10-diol cannot simultaneously be bonded to the nickel peroxide surface.[8]

We conclude that in the oxidation reaction of 1,2-glycols with nickel peroxide two types of reaction occur competitively; the first type is an ordinary radical reaction beginning with α-hydrogen abstraction to produce diones, and the second is a concerted noncyclic mechanism on the two reaction site to yield C–C bond cleavage products.

Experimental Section

Materials.—*meso*-Hydrobenzoin and benzylphenylcarbinol were prepared from benzil and desoxybenzoin respectively by reduction with lithium aluminum hydride, and *meso*-1,2-diphenyl-1,2-dideuterioethane-1,2-diol and *meso*-2,3-dideuteriobutane-2,3-diol from benzil and biacetyl respectively with lithium aluminum deuteride, essentially according to the literature. Both deuterized compounds were confirmed by infrared spectrometry. Decahydronaphthalene-*cis*-9,10-diol was prepared from 1,2,3,4,5,6,7,8-octahydronaphthalene with osmium tetroxide, and the trans isomer by the oxidation of the octahydronaphthalene with *m*-chloroperbenzoic acid in a similar method of Shani and Sondheimer[9] followed by the treatment with acetic acid.[10] 1,2-Diphenylpropyl alcohol was synthesized from desoxybenzoin with methyl iodide and sodium ethoxide followed by the reduction with sodium borohydride. *cis*-Cyclopentane-1,2-diol was prepared by the oxidation of cyclopentene obtained from cyclopentanol and phosphoric acid, with potassium permanganate.[11] *trans*-Cyclopentane-1,2-diol was prepared by the oxidation of cyclopentene with hydrogen peroxide and formic acid.[12] Nickel peroxide was prepared by the method of Nakagawa, Konaka, and Nakata,[3] and its available oxygen content was 0.318×10^{-2} g-atom/g. *meso*-Butane-2,3-diol was commercially available.

Oxidation of *meso*-Hydro- and *meso*-Deuteriobenzoin with Nickel Peroxide.—A mixture of 0.032 mmol of *meso*-hydrobenzoin and 10 equiv of nickel peroxide was stirred vigorously by a magnetic stirrer in 34 ml of ether for 15 min at 30, 1, and −11°. After filtering off the nickel compound, the reaction mixture was analyzed by glpc (Schimazu GC-1B) to determine the yield of benzaldehyde and benzil (benzaldehyde, 30% silicone DC 550 column, 150° column temperature, ethylbenzene internal standard; benzil, 5% SE-30 column, 200° column temperature, benzophenone internal standard). *meso*-1,2-Diphenyl-1,2-dideuterioethane-1,2-diol was oxidized under the exactly same conditions and analyzed in the same way as described above. Benzaldehyde isolated from the reaction mixture in this oxidation reaction was confirmed to be C_6H_5CDO by infrared spectrometry.

Reaction of *meso*-Hydrobenzoin with Azoisobutyronitrile.—A solution of 0.6 mmol of *meso*-hydrobenzoin and 0.9 mmol of azoisobutyronitrile in 20 ml of benzene was heated at 65–70° for 1 hr under the nitrogen atmosphere. The reaction mixture was analyzed by the glpc method, used in the case of the oxidation with nickel peroxide, to determine a 21.4% yield of benzil, a 76.1% recovery of *meso*-hydrobenzoin, and no benzaldehyde.

Oxidation Rate of 1,2-Glycols and Related Compounds with Nickel Peroxide.—Two techniques were applied depending on the order of the reaction rate involved. The oxidation reaction rates of *meso*-hydrobenzoin and *meso*-1,2-diphenyl-1,2-dideuterioethane-1,2-diol, which are too fast to follow by the glpc method, were measured by the thermoanalytical technique developed by Takashima, Yoneyama, and Watanabe,[5] in which the change of reaction heats was followed on stirring a solution of 3 mmol of the substrate and 5 equiv of nickel peroxide in 150 ml of benzene with vigorous and constant rotation at 31°.

The reaction rates of *meso*-butane-2,3-diol, *meso*-2,3-dideuteriobutane-2,3-diol, benzylphenylcarbinol, and *cis*- and *trans*-cyclopentane-1,2-diol were measured by following the diol or the alcohol in the reaction mixture which resulted from oxidation of the substrate with 5 equiv of nickel peroxide in ether, using glpc for analysis [column, 5% PEG (*meso*-butane-2,3-diol, *cis*- and *trans*-cyclopentane-1,2-diol), Carbowax (benzylphenylcarbinol), 5% DEGS (benzhydrol, decahydronaphthalene-*cis*-9,10-diol, 1,2-diphenylpropyl alcohol); internal standard, naphthalene (*meso*-butane-2,3-diol), azobenzene (benzylphenylcarbinol, benzhydrol), acenaphthene (*cis*- and *trans*-cyclopentane-1,2-diol), benzophenone (decahydronaphthalene-*cis*-9,10-diol), benzil (1,2-diphenylpropyl alcohol)].

All oxidation reaction rates were expressed by the pseudo-first-order reaction rate equation. The measurements of the reaction rates were repeated two or three times. For example, we obtained 3.5 and 4.1×10^{-2} sec^{-1} in the oxidation of *meso*-hydrobenzoin, and 6.2, 5.6, and 4.2×10^{-4} sec^{-1} in the case of benzhydrol. In addition, the Arrhenius plots in the oxidation of *meso*-hydrobenzoin showed a straight line to give the activation energy of 5.69 kcal/mol, though it was derived from only three temperatures over a range of only 20°.

It was found that mainly acetaldehyde was produced on the oxidation of *meso*-butane-2,3-diol with nickel peroxide, but biacetyl, which is not converted to acetaldehyde by nickel peroxide, was not produced. The oxidation products of benzylphenylcarbinol were acetaldehyde and benzil. The initial major oxidation product from *cis*- and *trans*-cyclopentane-1,2-diol with nickel peroxide was glutaraldehyde, confirmed as the 2,4-dinitrophenylhydrazone.

Registry No.—Nickel peroxide, 1313-99-1; *cis*-cyclopentane-1,2-diol, 5057-98-7; *trans*-cyclopentane-1,2-diol, 5057-99-8.

(7) L. J. Heidt, E. K. Gladding, and C. B. Purves, *Paper Trade J.*, **121**, 35 (1945); *Chem. Abstr.*, **40**, 546 (1946).

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Reactions of Aryl Grignard Reagents with Pyridine 1-Oxide. The Structure of the Addition Products

T. J. VAN BERGEN AND RICHARD M. KELLOGG*

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

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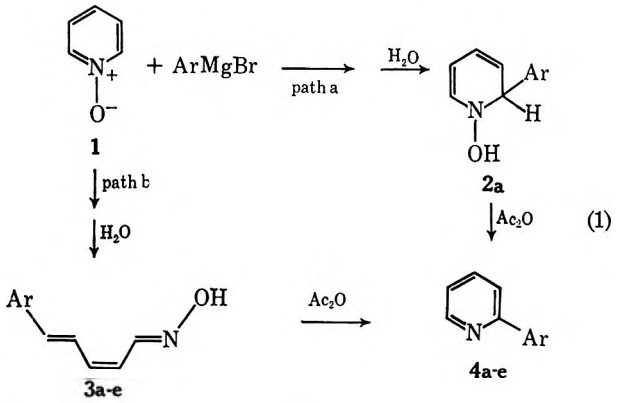
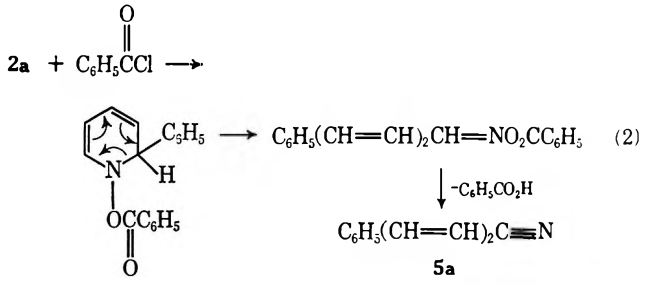
Addition of phenyl Grignard reagent to pyridine 1-oxide (**1**) leads to an addition product to which Kato and Yamanaka assigned 1,2-dihydropyridine structure **2a** (eq 1, path a).[1] This structural assignment ap-



(1)

a, Ar = phenyl
b, Ar = perdeuteriophenyl
c, Ar = 4-tolyl
d, Ar = 4-anisyl
e, Ar = 2-thienyl

peared to be supported by the conversion of presumed **2a** to 2-phenylpyridine (**4a**) upon treatment with acetic anydride. Kato and coworkers[2] have also shown that the addition product is a useful intermediate for the synthesis of some *ring-opened* conjugated systems suggested to be formed along the general lines detailed in eq 2 for nitrile **5a** (which, after having been worked up,



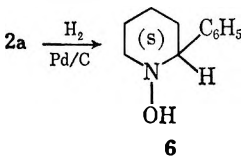
(2)

was identical with the presumed *all-trans*-**5a** prepared by another route).

We have been interested in 1,2-dihydropyridines[3a,b] and in the synthesis of arylpyridines[3c] and hence were led to use the Grignard addition to **1** described by Kato and Yamanaka. Although able to duplicate fully the results of these authors, we offer evidence here that the additions of phenyl, perdeuteriophenyl, 4-tolyl, 4-anisyl, or 2-thienyl Grignard reagents to pyridine 1-oxide lead not to 1,2-dihydropyridines **2** but rather to ring-opened products **3a–e** (eq 1, path b) and that subsequent transformations of **3** give 2-arylpyridines **4** as well as nitriles **5**.

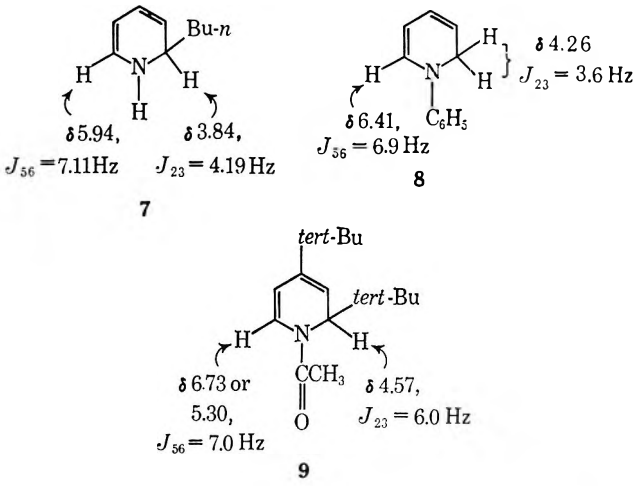
Results

Phenyl, 4-tolyl, 4-anisyl, and 2-thienyl Grignard reagents with **1** give addition products in 10–45% yield. No attempt was made to increase yields. The addition products all have the same general spectral features indicating like structural arrangement. Several details concerning the adduct of phenyl Grignard reagent and **1** militate against the proposed 1,2-dihydropyridine structure **2a**. Complete hydrogenation of **2a** should give **6** (eq 3). Kato and Yamanaka[1] obtained a compound, mp 57–58°; authentic **6** has mp 111–112°.[4]



(3)

The nmr spectrum of supposed **2a** shows one proton at δ 8.5 (J = 10 Hz) which is suggested to be 2 H.[1] Comparison with known 1,2-dihydropyridines **7–9**[5–7] shows this J value to be unreasonably large for J_{23} and the absorption to be shifted too far downfield for a dihydropyridine, even assuming that it arises from the 6 rather than the 2 proton.



Our structural assignment of 5-phenyl-2(*cis*),4-(*trans*)-pentadienal (*syn*)-oxime (**3a**) to Kato and Yamanaka's addition product is based primarily on the nmr spectrum. Other spectral data are also in full agreement with this structure. To simplify the nmr spectrum of the addition product, Grignard addition to **1** was carried out using bromobenzene-d_5. A product, mp 127.5–129°, was obtained whose 100-Mc nmr spectrum is shown in Figure 1 along with the computer-simulated spectrum derived using the spectral param-

(1) T. Kato and H. Yamanaka, *J. Org. Chem.*, **30**, 910 (1965), and references to earlier work contained therein.

(2) T. Kato, H. Yamanaka, T. Adachi, and H. Hiranuma, *ibid.*, **32**, 3788 (1967).

(3) (a) R. M. Kellogg, T. J. van Bergen, and H. Wynberg, *Tetrahedron Lett.*, 5211 (1969); (b) T. J. van Bergen and R. M. Kellogg, *J. Org. Chem.*, **36**, 978 (1971); (c) H. Wynberg, T. J. van Bergen, and R. M. Kellogg, *J. Org. Chem.*, **34**, 3175 (1969).

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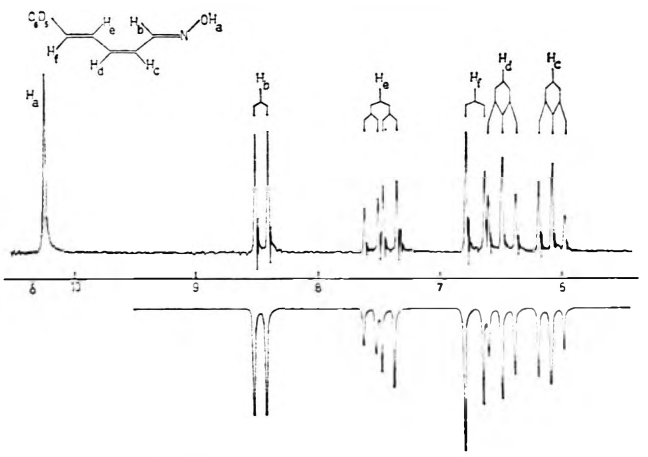
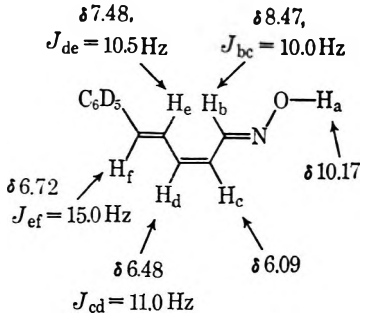


Figure 1.—100-Mc nmr spectrum (upper) of **3b** at *ca.* 37° in C_3D_6O. The negative signal spectrum (lower) is computer simulated using the parameters given in the text.

eters shown below. The sharp melting point and cleanness of the nmr spectrum indicate formation of a single isomer. The large coupling constants derived from the nmr spectrum immediately suggest olefinic units; this, coupled with straightforward chemical considerations, requires the general structural unit **3b**. Detailed configurational and conformational assignments can be made from further dissection of spectral data. The anomalous (for **2a**) low field doublet at δ 8.47 should logically arise from the proton adjacent to N



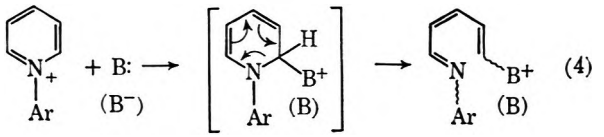
(H_b); H_b was shown furthermore to be coupled to a proton absorbing at δ 6.09 which must be H_c. The other simple doublet at δ 6.72 must come from the proton H_f adjacent to phenyl and the magnitude of the coupling constant (J = 15.0 Hz) requires that H_f and H_e define a trans double bond (Δ^4).[8] The Δ^2 double bond defined by H_d and H_c should be cis on the basis of J_{cd} = 11.0 Hz.[8] This assignment is also supported by absorptions at 845 and 785 cm^{-1} in the ir.[9] Finally, the values of J_{de} and J_{cd} are consistent for a transoid conformation as shown in **3b**.[10-12] This entire configurational and conformational assignment is strengthened further by the observation of a nuclear Overhauser effect (NOE) between H_b and H_e. Irradiation of H_b enhances the absorption of H_e 20% while other integrations are not affected. The closest approach of the nuclear centers of H_b and H_e in **3** is 1.8 Å measured from models.

Chemical considerations require the presence of the oxime functionality which explains the downfield shift of the absorption for H_b which is perfectly reasonable for an oxime.[13] Assignment of the syn configuration[14a] is based on the value $\delta_{OH} - \delta_{H_b}$ in DMSO.[14b] For a considerable sample of aliphatic oximes the chemical shift difference between the OH and vinylic protons is 3.04–3.18 for *syn*-oximes and 3.82–4.23 for *anti*-oximes. For two aromatic oximes the respective differences are 2.95–3.01, syn; 3.96–4.61, anti. For **3** (phenyl or perdeuteriophenyl) $\delta_{OH} - \delta_{H_b}$ is 2.56 and for the 4-anisyl, 4-tolyl, and 2-thienyl derivatives the value varies from 2.58 to 2.75. This strongly suggests syn configuration for the oxime functionality.

The net conclusion is that Grignard additions to pyridine 1-oxide result in ring opening leading stereospecifically to a Δ^2-*cis*,Δ^4-*trans*-pentadienal *syn*-oxime; the 1,2-dihydropyridine isomer is not formed in isolable amounts.

Discussion

The well-known ring openings (eq 4) of various *N*-arylpyridium salts on reaction with hydroxide ion or



(4)

other bases serve as obvious precedent for the reactions of **1**.[15] For the special case that the nucleophile is an aryl amine, ring opening is followed by ring closure resulting in a new pyridium salt and elimination of $ArNH_2$ (Ar is usually substituted with electron-withdrawing groups).[16-18] The ring closure, which takes place only with the neutral form of the open precursor,

(8) A. A. Bothner-By and R. K. Harris, *J. Amer. Chem. Soc.*, **87**, 3445 (1965).

(9) See, for example, K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, and references cited therein.

(10) D. P. Kelly, *J. Mol. Spectrosc.*, **28**, 204 (1968).

(11) J. A. Elvidge and L. M. Jackman, *Proc. Chem. Soc., London*, 89 (1959).

(12) A. L. Segre, L. Zetta, and A. Di Corato, *J. Mol. Spectrosc.*, **32**, 296 (1969).

(13) G. C. Kleinspehn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, **32**, 460 (1967).

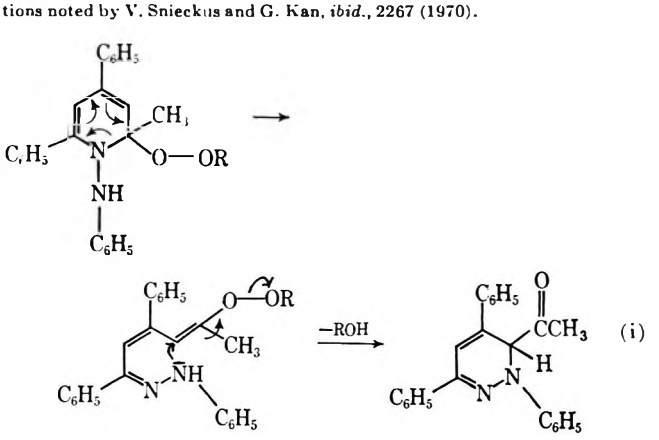
(14) (a) A review of oxime chemistry: C. G. McCarty in "The Chemistry of the Carbon Nitrogen Double Bond," S. Patai, Ed., Interscience, New York, N. Y., 1970, pp 383–392. (b) F. A. Neugebauer, *Tetrahedron Lett.*, 2345 (1970).

(15) Reviews: (a) R. A. Barnes, "Pyridine and Its Derivatives," Vol. I, E. Klingsberg, Ed., Interscience, New York, N. Y., 1960, p 57; (b) E. N. Shaw, "Pyridine and Its Derivatives," Vol. II, E. Klingsberg, Ed., Interscience, New York, N. Y., 1961, p 32; (c) Y. Taumura and N. Tsujimoto, *Chem. Ind. (London)*, 926 (1970).

(16) Original literature: Th. Zincke, *Justus Liebigs Ann. Chem.*, **330**, 361 (1903); *ibid.*, **333**, 296 (1904).

(17) For a recent example of a closely related reaction, see S. L. Johnson and K. A. Rumon, *Tetrahedron Lett.*, 1721 (1966).

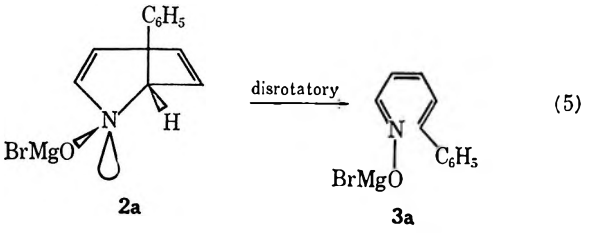
(18) A closely related set of reactions (eq i) is likely involved in reactions noted by V. Snieckus and G. Kan, *ibid.*, 2267 (1970).



(i)

is suggested to be an electrocyclic reaction on the basis of detailed mechanistic studies.[19]

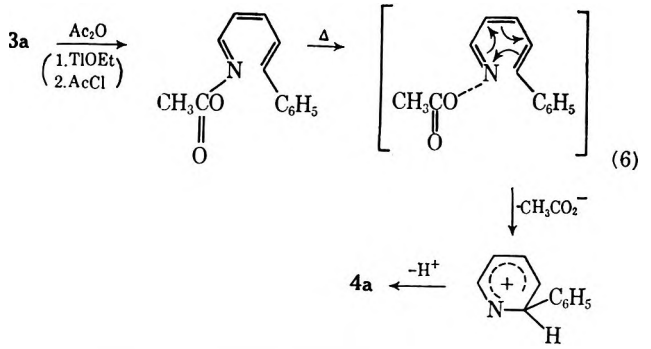
Although ring openings of pyridine 1-oxides seem not to have been noticed previously, such behavior should not occasion surprise.[20] An important driving force for ring opening is likely the potentially greater delocalization of charge in the open-chain structure. It is tempting to suppose that, subsequent to addition to Grignard reagent perpendicular to the pyridine ring, immediate disrotatory opening[21] of conformation **2a** occurs (at a rate faster than conformational equilibrium) leading directly to the observed stereochemistry (eq 5). The possibility that the *anti*-oxime as its magnesium salt isomerizes spontaneously to the syn form cannot be disregarded, however.



2a **3a** (5)

The facile ring closure of compounds **3** upon treatment with acetic anhydride (a small amount of nitriles **5** is also formed) may be viewed as a Beckmann-like reaction (eq 6). Treatment of the thallium salt of **3a** gives the acetate[22,23] which undergoes smooth ring closure in dioxane solution; hence the reaction sequence as depicted in eq 6. A minor variation on eq 6 would involve electrocyclic cyclization of **3** with subsequent loss of acetic acid.[19,24,25]

Possible synthetic utility of the products **3** is obvious particularly since an otherwise difficult to obtain cis double bond can be secured selectively. Considerable care in subsequent manipulations is called for, however, because of the possibility of rapid cis–trans isomerism



(6)

in these types of compounds.[26] In this connection, Kato, *et al.*,[2] isolated from **3a**, on treatment with benzoyl chloride, two compounds, mp 78.5–79.5 and 157–158°. They suggest that the lower melting compound is the benzoylated derivative of **2a** and the higher melting isomer to be a derivative of (presumably) *all-trans*-**3a**. Most likely the former compound is actually a derivative of Δ^2-*cis*,Δ^4-*trans*-**3a** while the latter is a derivative of Δ^2-*trans*,Δ^4-*trans*-**3a**.

Experimental Section

Melting points were measured on a calibrated melting point block. Nmr spectra (60 Mc) were taken with a Varian A-60 instrument. Ultraviolet spectra were run on a Zeiss PMQ-II spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Model 21 instrument. Microanalyses were performed by the analytical department of this University under direction of Mr. W. Hazenberg. Bromobenzene-d_5 was obtained from Merck AG, Darmstadt, Germany.

5-Aryl-2(*cis*),4(*trans*)-pentadienal (*syn*)-oximes (3a–e) were obtained by adding dropwise a solution of 6.0 g (0.07 mol) of **1** in 50 ml of dry tetrahydrofuran (THF) to a well-stirred Grignard reagent (0.10 mol), held at room temperature and prepared from the aryl bromide or iodide in 50–75 ml of dry THF. Stirring was continued for 1 hr after all the pyridine *1*-oxide had been added. The reaction mixture was poured out into concentrated ammonium chloride solution and the aqueous portion was extracted twice with THF.

The combined organic layers were concentrated by evaporating the solvent, and the residue was dissolved in methylene chloride and was dried over Na_2SO_4. Filtration and removal of the solvent yielded an oily residue from which the solid oxime separated upon crystallization from benzene, toluene, or methylcyclohexane. Crystalline **3d** was obtained only with difficulty by this procedure. A second recrystallization was necessary in all cases to obtain analytical samples. See Table I for physical and other data.

5-(Phenyl-d_5)-2(*cis*),4(*trans*)-pentadienal (*syn*)-oxime (3b) was isolated from the reaction of the Grignard reagent, prepared from 7.3 g of bromobenzene-d_5 and 1.4 g of magnesium in 25 and 40 ml of dry THF, respectively, with 2.7 g of **1** in 25 ml of the same solvent. By following the procedure described above, 1.7 g of **3b** was obtained.

5-Aryl-2,4-pentadiene nitriles (5a–e) were isolated from the reaction of an ice-cooled solution of 2.8 mmol of the oxime in 10 ml of dry pyridine and 2.8 mmol (0.5 g) of tosyl chloride. The solution was stored overnight in a refrigerator. Most of the pyridine was removed at reduced pressure. The residue was dissolved in methylene chloride, extracted three times with water, dried (Na_2SO_4), filtered, and concentrated by chromatography on a silica gel column with a 1:1 mixture of benzene and diethyl ether as the eluent. Further purification was effected by distillation or crystallization from methylcyclohexane. For physical constants and other data see Table II.

Ring closure of 5-phenyl-2(*cis*),4(*trans*)-pentadienal (*syn*)-oxime (3a) to 2-phenylpyridine was observed when 0.5 g of **3a** in 7 ml of acetic anhydride was refluxed for 1 hr. The solvent was evaporated and the residue dissolved in diethyl ether. This solution was extracted with water, dried (Na_2SO_4), filtered, and

(19) (a) E. N. Marvell, G. Caple, and I. Shahidi, *Tetrahedron Lett.*, 277 (1967); (b) E. N. Marvell, G. Caple, and I. Shahidi, *J. Amer. Chem. Soc.*, **92**, 5641 (1970); (c) E. N. Marvell and I. Shahidi, *ibid.*, **92**, 5646 (1970).

(20) For example, F. Binns and H. Suschitzky, *Chem. Commun.*, 750 (1970), report that methylmagnesium bromide adds to 2,3,4,5-tetrachloropyridine 1-oxide to give a 1,2-dihydropyridine which loses MgBrCl to give 2-methyl-3,4,5-trichloropyridine 1-oxide. No ring opening is observed. We are grateful to Professor Suschitzky for correspondence on this problem.

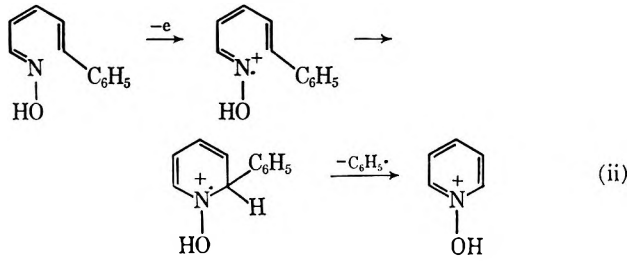
(21) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

(22) E. C. Taylor, G. H. Hawks, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968); E. C. Taylor, C. W. McLay, and A. McKillop, *ibid.*, **90**, 2422 (1968).

(23) Oxime acetates from ketoximes are formed spontaneously at room temperature upon treatment with acetic anhydride: E. J. Corey and J. E. Richman, *ibid.*, **92**, 5276 (1970), and references cited therein.

(24) This represents a drastically improved route to 2-(2′-thienyl)pyridine (**4e**) obtained only with difficulty by other methods.[3c]

(25) Analogous behavior may occur in the mass spectrometer. The 100% peak from **3a** is seen at *m/e* 96 consistent with the process detailed in eq ii, whereby, subsequent to ionization at nitrogen, ring closure occurs followed by expulsion of a phenyl radical giving the observed fragment. For the mass spectra of dihydropyridines, see G. Schroll, S. P. Nygaard, S. O. Lawesson, A. M. Duffield, and C. Djerassi, *Ark. Kemi*, **29**, 525 (1969).



(ii)

(26) (a) G. Gamboni, V. Theus, and H. Schinz, *Helv. Chim. Acta*, **38**, 225 (1955); (b) E. E. Boehm and M. C. Whiting, *J. Chem. Soc.*, 2541 (1963).

TABLE I

PHYSICAL PROPERTIES OF 5-(ARYL)-2(*cis*),4(*trans*)-PENTADIENAL (*syn*)-OXIMES (**3a–e**)

				Uv[b]		Nmr[c]						Calcd			Found		
Compd	Mp, °C	Yield, %	Ir,[a] cm^{-1}	mμ	Log ε	δ_{H_a}	δ_{H_b}	δ_H[j]	δ_{CH_3}	$J_{H_bH_c}$ in Hz	C	H	N	C	H	N
3a	128.5–130.5[d]	28	845, 785	237	4.13	11.09	8.53	5.80–7.80		10.0	76.29	6.40	8.09	76.43	6.15	8.24
				302 (s)[g]	4.51									76.59	6.44	8.13
				315	4.61											
				328 (s)	4.57											
3b	127.5–129[d]	27	840, 790	237	4.17	11.16	8.56	5.80–7.70		10.5	74.13	3.40	7.86	74.15	3.49	7.83
				300 (s)	4.52							D[i]		74.31	3.57	7.89
				314	4.62							5.65			D[i]	
				327	4.52										5.24	
															5.35	
3c	128–130[e,f]	45	870, 780	241	4.07	11.11	8.52	5.80–7.70	2.30	10.0	76.98	7.00	7.48	77.11	6.90	7.36
				310 (s)	4.45									77.29	6.96	7.27
				320	4.53											
				332	4.45											
3d	119–121[d]	10	860, 775	245	4.05	11.11	8.53	5.80–7.70	3.69	10.0	70.91	6.44	6.89	71.15	6.30	6.89
				328	4.59									71.10	6.32	6.89
3e[h]	110–112[e]	48	860, 785	250	4.29	11.16	8.41	5.85–7.60		10.0						
				332	4.71											
				345	4.67											

[a] KBr pellet. [b] In 96% ethanol. [c] In dimethyl sulfoxide-d_6. [d] Recrystallized from benzene. [e] Recrystallized from toluene. [f] Recrystallized from methylcyclohexane. [g] Shoulder. [h] Repeated attempts to obtain a good analysis failed. [i] Deuterium. [j] For aromatic and vinylic protons.

TABLE II

PHYSICAL PROPERTIES OF 5-(ARYL)-2,4-PENTADIENENITRILES (**5**)[a]

				Uv[b]		Nmr[c]				Calcd, %				Found, %			
Ar	Mp or bp (mm), °C	Yield, %	Ir, cm^{-1}	mμ	Log ε	δ_{H_a}	δ_{other}	δ_{CH_3}	$J_{H_aH_b}$ in Hz	C	H	N	S	C	H	N	S
5a	104–105	80	2200	232	4.04	5.18	6.60–7.60		8.0	85.13	5.85	9.03		84.95	5.89	8.92	
	(0.3)			307	4.50									85.06	5.77	8.95	
5b	105–107	67	2210	232	4.08	5.18	6.60–7.50		8.0	82.48	2.51	8.74		82.55	2.53	8.65	
	(0.3)			307	4.56						D[e]			82.67	2.53	8.76	
											6.30				D[e]		
															6.32		
															6.32		
5e	25.0–26.3	80	2210	236	3.97	5.13	6.70–7.40		8.0	67.04	4.38	8.69	19.88	66.87	4.38	8.81	19.95
				337	4.44									66.96	4.40	8.83	19.93
5c	54.5–55.5	85	2200[d]	237	4.05	5.16	6.70–7.50	2.37	9.0	85.16	6.55	8.28		84.73	6.51	8.49	
				244	3.95									84.91	6.58	8.48	
				318	4.50												

[a] Probably cis-trans mixtures. [b] In 96% ethanol. [c] In carbon tetrachloride. [d] KBr pellet. [e] Deuterium.

concentrated. The remaining oil was purified by chromatography over a silica gel column. Elution with benzene yielded 59 mg (13%) of an oil spectroscopically identified as **5a**. Elution with diethyl ether gave 272 mg (60%) of 2-phenylpyridine (**4a**) as confirmed by comparison with an authentic sample.[27]

Ring closure of 5-(2-thienyl)-2(*cis*),4(*trans*)-pentadienal (*syn*)-oxime (3e) to 2-(2′-thienyl)pyridine was performed as described above with the modification that the reflux period was 15 min. Starting with 0.7 g of **3e**, 104 mg (17%) of **5e** (identified spectroscopically) and 309 mg (49%) of a solid, mp 60–61.5° (recrystallized from petroleum ether, bp 40–60°), identical with 2-(2′-thienyl)pyridine **3e**, were isolated.

Acetylation of 5-phenyl-2-(*cis*),4(*trans*)-pentadienal (*syn*)-oxime (3a) was achieved *via* the thallium salt of **3a** which was prepared by adding a 4.9-g solution of thallium ethoxide[22] in 20 ml of dry diethyl ether to a 3.5-g solution of **3a** in 50 ml of the same solvent. The precipitated yellow salt, mp 137–140°, was collected in an almost quantitative yield by filtration and subsequent washing with diethyl ether.

To a well-stirred suspension of 2.0 g of this compound was added dropwise a solution of 420 mg of freshly distilled acetyl chloride over a 1-hr period maintaining the temperature at 5°. The color changed slowly to a pale yellow. Stirring was continued for 15 min. After all the acetyl chloride had been added, the thallium chloride was filtered off and the filtrate was concentrated at room temperature at reduced pressure to avoid decomposition of the product. The residue, 1.05 g (90%) of the almost pure acetylated oxime, could not be obtained in crystalline form and was immediately used for further reaction.

The oxime acetate had uv max (96% EtOH) λ_{max} 237 mμ (log ε 3.94) and 319 (4.49); ir 1770 (C=O) and 1010 cm^{-1} (NO); nmr (CCl_4) δ 2.11 (s, 3, CH_3), 6.00–7.50 (m, 9, aromatic and vinylic H), 8.48 (d, 1, J = 10.0 Hz, CH=N).

Ring closure of acetylated 3a to 2-phenylpyridine was observed when 445 mg of the acetate was concentrated by flash evaporation and the residue was purified by preparative thick layer chromatography (silica gel and benzene). A trace of 5-phenyl-2,4-pentadienenitrile and 133 mg (41%) of an oil identical with authentic 2-phenylpyridine[27] were isolated.

Reactions of *tert*-butylmagnesium bromide and methylmagnesium iodide with 1 were carried out in respectively THF and diethyl ether as described for the aryl compounds. Although a reaction undoubtedly took place, no products could be isolated.

Phenyllithium was allowed to react with **1** in THF at different temperatures in the same manner as described for the Grignard reagents. Only tarry mixtures were obtained in which no oxime could be detected and from which only a small amount of biphenyl was isolated.

Registry No.—**1**, 694-59-7; **3a**, 28541-47-1; **3b**, 28541-48-2; **3c**, 28541-49-3; **3d**, 28541-50-6; **3e**, 28541-51-7; **5a**, 14164-31-9; **5b**, 28541-53-9; **5c**, 28541-54-0; **5e**, 28541-55-1.

Acknowledgment.—We are grateful to Mr. C. Kruk of the University of Amsterdam for measuring the 100-Mc nmr spectra and for both suggesting and carrying out the NOE experiments.

(27) K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931).

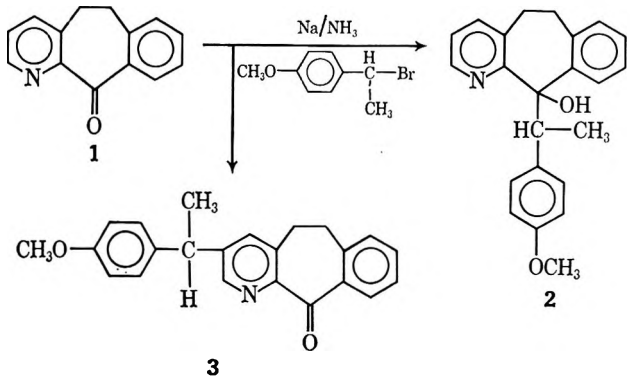
An Anomalous Alkylation of a Pyridine System[1]

FRANK J. VILLANI,*[2a] CLAIRE A. ELLIS,[2a] MILTON D. YUDIS,[2b] AND JAMES B. MORTON[2b]

Schering Corporation, Bloomfield, New Jersey 07003

Received December 1, 1970

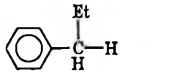
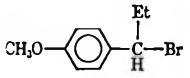
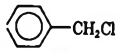
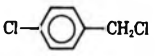
In the reductive alkylation[3] of the disodio derivative of 11*H*-5,6-dihydrobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one[1b,4] (**1**) with 1-*p*-anisyl-1-bromoethane, two products were consistently obtained. The expected tertiary carbinol **2** was the major product (65–70% yield) and a smaller amount (10–15%) of a novel alkylation product **3** was isolated. The products were separated



by column chromatography on alumina using mixtures of benzene–chloroform whereby the tertiary carbinol was eluted first. The isolation of **3**, albeit in low yield and under the stringent steric requirements of the alkylating agent as discussed later, was unexpected in view of the known difficulty in alkylation of the β position of the pyridine ring.[5] Compound **3** shows strong carbonyl absorption in the ir at 6.0 μ, and its structure was assigned on the basis of the nmr spectrum as follows (10% soluion in $CDCl_3$, shifts reported in parts per million from internal TMS): δ 1.66 (3 H, α-$CHCH_3$, d, J = 7 Hz), 3.18 (4 H, ethylene bridge, s, 2 Hz wide), 3.79 (3 H, OCH_3, s), 4.18 (1 H, $CHCH_3$, q, J = 7 Hz), 6.7–7.6 (8 H, 7 phenyl plus the γ-pyridyl proton), 8.06 (1 H, the proton peri to CO, m), 8.62 (1 H, α-pyridyl proton, d, $J_{\alpha,\gamma}$ = 2 Hz). The appearance of the α-pyridyl signal as a weakly coupled doublet clearly indicates substitution at the β-pyridyl position. The α-pyridyl proton in the nmr spectrum of carbinol **2** appears at δ 8.42 as a quartet coupled to the β and γ protons, $J_{\alpha,\beta}$ = 4.5 Hz and $J_{\alpha,\gamma}$ = 2 Hz, respectively.

Table I

Reductive Alkylation of 1[a]

Alkylating agent	Carbinol (type 2) % yield[b]	Carbinol (type 2) Registry no.	Carbinol (type 2) Mp, °C	Ketone (type 3) % yield	Ketone (type 3) Registry no.	Ketone (type 3) Mp, °C
	20	28795-67-7	101–102[c]	14	28795-72-4	94–95[c]
	24	28795-68-8	141–142[c]	17	28795-73-5	123–125[c]
	92	29795-69-9	84–85[d]			
	72	28795-70-2	109–110[d]			
$(CH_3)_2CHBr$	56	28795-71-3	94–96[d]			

[a] Satisfactory analytical data (±0.35% for C, H, and N) were reported for all compounds except the ketone, mp 123–125°, from 1-anisyl-1-bromopropane (calcd, C, 80.64; found, C, 81.12): Ed. [b] Yields do not represent the maximum obtainable. The recorded yields represent only one experiment and intermediate fractions from the chromatography containing both carbinol and ketone fractions were discarded. Ir and nmr spectra are in agreement with the structures as described in the text. [c] Recrystallized from isopropyl ether. [d] Recrystallized from hexane.

Sodium borohydride reduction of the carbonyl group of **3** gave the expected secondary carbinol.

Reductive alkylation of **1** using other secondary aromatic halides as, for example, 1-bromo-1-phenylpropane and 1-bromo-*p*-anisylpropane gave similar results (see Table I). However, when this reaction was carried out with primary aromatic halides, benzyl chloride, or *p*-chlorobenzyl chloride, or with a secondary aliphatic halide, *e.g.*, isopropyl bromide, only the tertiary carbinol of type 2 was obtained in excellent yields.

A similar alkylation of the nonbridged ketone, 2-benzoylpyridine, with 1-*p*-anisyl-1-bromopropane gave exclusively the tertiary carbinol **4**.

Experimental Section[6]

General Procedure.—To a well-stirred solution of 5.0 g (0.22 g-atom) of sodium metal in 300–400 ml of anhydrous liquid

(1) (a) Derivatives of 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene and Related Compounds. IV. (b) For paper III, see F. J. Villani, P. J. Daniels, C. A. Ellis, T. A. Mann, and K. Wang, *J. Heterocycl. Chem.*, **8**, 73 (1971).

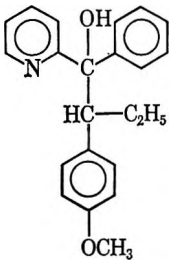
(2) (a) Department of Medicinal Chemistry; (b) Physical and Analytical Chemical Research Department.

(3) J. A. Gautier, M. Miocque, C. Fauran, and M. Duchon d'Engenières, *Bull. Chim. Soc.*, 3162 (1965).

(4) F. J. Villani, U. S. Patent 3,326,924 (1967).

(5) After this work was completed, two additional examples of β-alkylation of simple pyridine derivatives were described. See C. S. Giam and J. L. Stout, *Chem. Commun.*, 478 (1970); R. Levine and W. M. Kadunce, *ibid.*, 921 (1970).

(6) Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer Infracord and nmr spectra on a Varian A-60A spectrometer. Microanalyses were carried out by the Physical and Analytical Chemical Research Department of the Schering Corp.



4

ammonia was added dropwise a solution of 21 g (0.1 mol) of ketone **1** in 150 ml of tetrahydrofuran (THF) (dried over calcium hydride) and the dark blue-purple mixture was stirred for 15 min. A solution of 1-*p*-anisyl-1-bromoethane (0.15 mol) prepared in toluene as previously described[7] was added dropwise and the mixture was stirred for 6 hr. Ammonium chloride (10 g) was added and, after the ammonia had evaporated, the THF was removed *in vacuo* on steam bath. To the residue, water and benzene was added and the mixture was separated and extracted with benzene. The combined benzene solutions were extracted with dilute (10%) hydrochloric acid and, after preliminary washing with ether, the acid solution was made basic with ammonium hydroxide and extracted with chloroform. The dark brown oily residue after removal of the chloroform was chromatographed on 650 g of alumina using benzene as the eluting agent; fractions of 650–700 ml were collected. Carbinol **2** [22.7 g (66%)] was obtained in the first three fractions. After an additional 2 l. of benzene was collected, the solvent was changed to 50% benzene–chloroform and an additional seven fractions were collected. Finally 100% chloroform was used to elute the last traces of ketone **3**.

Carbinol 2 was recrystallized from hexane, mp 103–105°, and showed a strong OH absorption at 3.1 μ.

Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 79.84; H, 6.93; N, 4:30.

Ketone 3 was recrystallized from hexane, mp 114–116°, ir 6.0 μ.

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.56; H, 5.82; N, 4.03.

2-(*p*-Anisyl)-1-phenyl-1-(2-pyridyl)butanol (4).—Using the same procedure, this compound was obtained in 46% yield from 2-benzoylpyridine and 1-(*p*-anisyl)-1-bromopropane, mp 120–121° from hexane.

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.29; H, 6.95; N, 4.20. Found: C, 79.18; H, 6.94; N, 3.90.

Reduction of 3.—Ketone **3** (0.3 g) was dissolved in 15 ml of methanol and 0.2 g of sodium borohydride was added at 0–5°. After 2.5 hr the methanol was removed, water was added, and the product was extracted with chloroform. After removal of the solvent, the residue was recrystallized twice from petroleum ether (bp 30–90°), mp 118–122°.

Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.01; H, 6.90; N, 3.80.

Registry No.—**2**, 28795-63-3; **3**, 28795-64-4; **3** (reduced), 28795-65-5; **4**, 28795-66-6.

(7) F. J. Villani, C. A. Ellis, R. F. Tavares, M. Steinberg, and S. Tolksdorf, *J. Med. Chem.*, **13**, 359 (1970).

A Novel Synthesis of Benzylamines from Benzaldehydes

GEORGE P. RIZZI

The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

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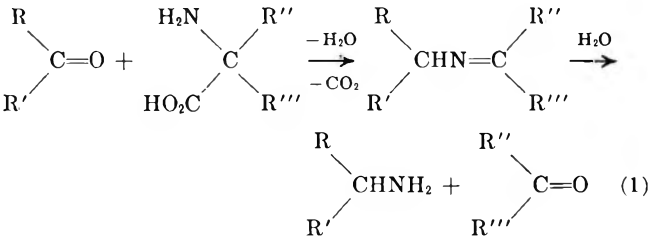
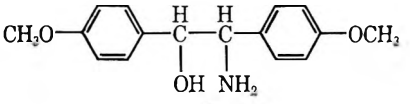
Because of their biological significance, the reactions of α-amino acids with carbonyl compounds have been widely studied.[1] It is unfortunate however, that only a few reports on this subject have dealt with these reactions from the synthetic chemist's point of view. A potentially useful but infrequently cited method for reductively aminating aldehydes and ketones is the reaction of carbonyl compounds with α-disubstituted amino acids under decarboxylation conditions followed by hydrolysis (eq 1).

The principal advantage of this method is that it accomplishes in essentially one step what is normally considered a two-step synthesis, *e.g.*, conversion of an aldehyde to an oxime, azine, phenylhydrazone, etc.,[2,3] followed by chemical reduction. Also, because the method does not require molecular hydrogen it should lend itself to selective reductive amination of an aldehyde function in the presence of otherwise reducible groups.



(1)

In 1964 Chatelus reported that the reaction of 2-amino-2-methylbutyric acid (isovaline) in fourfold molar excess of anisaldehyde gave *p*-methoxybenzylamine in quantitative yield.[4] In spite of the inherent simplicity in carrying out this reaction, we were not able to reproduce the yield claimed. Instead, we repeatedly isolated only 30–50% of *p*-methoxybenzylamine together with varying amounts of diastereomeric mixtures of alkamines **1**. This result was not too surprising since other workers had employed similar conditions (excess aldehyde) for the express purpose of synthesizing various alkamines.[5]



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In this note we wish to describe an improved process for reductive amination of benzaldehydes in which a single mole of aldehyde is used per mole of amino acid. The method consists of slowly adding benzaldehyde or a substituted benzaldehyde to a refluxing slurry of commercially available *dl*-isovaline in dimethylformamide (DMF). Carbon dioxide is evolved rapidly during the addition and a nearly clear solution results shortly after all the aldehyde is added. DMF is removed by simple distillation or *via* a rotatory film evaporator, and the residue is boiled with 2 *N* HCl to hydrolyze the imine intermediate. In this way a benzylamine hydrochloride is formed in high

(1) A. F. Al-Sayyab and A. Lawson, *J. Chem. Soc. C*, 406 (1968); J. Gebert and B. v. Kerékjártó, *Justus Liebigs Ann. Chem.*, **718**, 249 (1968); G. D. Kalyankar and E. E. Snell, *Biochemistry*, **1**, 594 (1962); K. Dose, *Chem. Ber.*, **90**, 1251 (1957); D. E. Metzler, M. Ikawa, and E. E. Snell, *J. Amer. Chem. Soc.*, **76**, 648 (1954).

(2) W. S. Emerson, *Org. React.*, **4**, 174 (1948).

(3) H. Feuer and D. M. Braunstein, *J. Org. Chem.*, **34**, 1817 (1969).

(4) G. Chatelus, *Bull. Soc. Chim. Fr.*, 2523 (1964).

(5) D. Ll. Hammick, *et al.*, *J. Chem. Soc.*, 3825 (1953); E. Takazi, H. Ichikawa, and I. Ensaka, *J. Pharm. Soc. Jap.*, **71**, 652 (1951) [*Chem. Abstr.*, **46**, 8045 (1952)].

yield. The salt may be separated and purified at this stage or alternatively the crude reaction mixture can be treated with sodium carbonate and the free amine extracted with solvent. Results obtained with several benzaldehydes are shown in Table I. Our

TABLE I
AMINES FROM REDUCTIVE AMINATION OF BENZALDEHYDES

Aldehyde[a]	Amine product	% yield[b,c]	Bp, °C (mm)
Benzaldehyde	Benzylamine	59	182–184 (atm)[d]
p-Methoxybenzaldehyde	*p*-Methoxybenzylamine	64	121–123 (14)[e]
o-Chlorobenzaldehyde	*o*-Chlorobenzylamine	70	99.5–102 (11)[f]
p-Chlorobenzaldehyde	*p*-Chlorobenzylamine	77	106–108 (11–12)[g]

[a] Liquid aldehydes were freshly distilled before use; *p*-chlorobenzaldehyde was employed as a 50% solution in DMF. [b] Yields are based on weights of distilled amines. [c] Product infrared spectra were identical with spectra of known, commercially available amines. [d] Lit. bp 184° [J. L. E. Erickson, *Chem. Ber.*, **59**, 2665 (1926)]. [e] Lit. bp 122–124° (14 mm) [M. Tiffeneau, *Bull. Soc. Chim. Fr.*, **9**, 819 (1911)]. [f] Lit.[8] bp 103–104° (11 mm). [g] Lit. bp 106–107° (15 mm) [J. v. Braun, M. Kühn, and J. Weismantal, *Justus Liebigs Ann. Chem.*, **449**, 249 (1926)].

yields compared favorably with those obtained in other reductive aminations of aromatic aldehydes.[2]

When reactions were run without dropwise addition or when excess aldehyde was used as solvent, lower yields of benzylamines were obtained. The method was unsatisfactory for reductive amination of conjugated unsaturated aliphatic aldehydes.[6]

The reductive amination proceeded more slowly in diglyme. Thus, when 0.05-mol quantities of *p*-anisaldehyde and isovaline were refluxed in diglyme (30 ml), only 75% of the amino acid was consumed after 4 hr. Under these conditions the yield of *p*-methoxybenzylamine based on amino acid reacted was 62%. In this instance dropwise addition of aldehyde did not improve the yield of amine.

The reaction succeeded to a still lesser extent when isovaline was replaced with α-aminoisobutyric acid (α-methylalanine). When equimolar amounts of benzaldehyde and α-aminoisobutyric acid were refluxed in diglyme (40 ml) for 2.7 hr, 57% of the amino acid was consumed and the yield of benzylamine based on amino acid reacted was only 31%.

Experimental Section[7]

General Procedure for the Preparation of Benzylamines.—To a stirred, refluxing slurry of *dl*-2-amino-2-methylbutyric acid (5.81 g, 0.0493 mol) in 30 ml of reagent grade DMF was added dropwise 5.34 ml (0.0490 mol) of redistilled [bp 92° (13 mm)] *o*-chlorobenzaldehyde. The aldehyde was added over a period of 20 min. After the addition, the mixture was refluxed 1 hr, cooled to 25°, and filtered to remove 0.22 g of unchanged amino acid. The filtrate was concentrated to a viscous syrup under vacuum and the syrup was hydrolyzed by boiling it with 100 ml of 2 *N* aqueous HCl for 2 hr. The cooled acidic solution was extracted with benzene to remove traces of colored impurities and the aqueous phase was concentrated to yield crude *o*-chlorobenzylamine hydrochloride. The crystalline residue was treated with *ca.* 50 ml of 5% Na_2CO_3 solution and extracted with ether to remove the benzylamine. The ether solution was dried (Na_2SO_4) and concentrated on a rotatory film evaporator, and the residue was distilled to give 4.86 g of *o*-chlorobenzylamine, bp 99.5–102° (11 mm) [lit.[8] bp 103–104° (11 mm)]. The liquid film ir of the product was identical with the ir of commercially available *o*-chlorobenzylamine.

Registry No.—Benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *o*-chlorobenzaldehyde, 89-98-5 *p*-chlorobenzaldehyde, 104-88-1.

(6) In the case of citral, only 10–15% of citralamine was obtained; most of the aldehyde was converted to higher boiling products.

(7) All boiling points were not corrected. Reactions involving aldehydes were performed under an atmosphere of prepurified nitrogen. Substituted benzaldehydes, benzylamines, and *dl*-isovaline were purchased from Aldrich Chemical Co. Infrared spectra were obtained on liquid film samples on a Perkin-Elmer Model 137 instrument.

(8) H. Franzen, *Chem. Ber.*, **38**, 1415 (1905).

Preparation of 1,4-Bis(*p*-tolylsulfonyl)-hexahydro-6-hydroxy-1*H*-1,4-diazepine and 1,4-Bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine

WALFRED S. SAARI,* ANDREW W. RAAB, AND STELLA W. KING

Merck Sharp and Dohme Research Laboratories, Division of Merck and Company, Inc., West Point, Pennsylvania 19486

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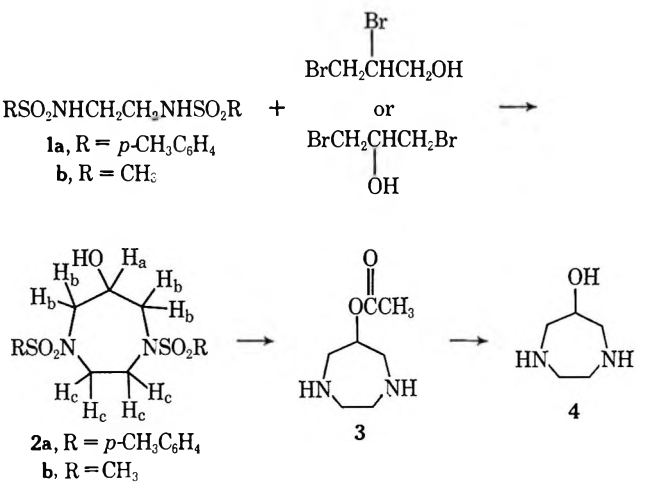
Synthesis of 1,4-bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine (**6a**) by reaction of the disodium salt of *N,N'*-ethylenebis(*p*-toluenesulfonamide) (**1a**) with 2,3-dibromo-1-propanol and conversion of the ditosylamide to 2-substituted piperazine derivatives has been reported several times.[1] We have found that the reaction of **1a** with 2,3-dibromo-1-propanol under these conditions gives only a small amount of the piperazine **6a**, the major product being the hexahydro-1*H*-1,4-diazepine **2a**.



Reaction of the disodium salt of **1a** with either 2,3-dibromo-1-propanol or 1,3-dibromo-2-propanol in ethanol gave the same hexahydro-1*H*-1,4-diazepine **2a**, mp 175–177°, in 56–59% yield. Initially the hexahydrodiazepine structure was assigned to **2a** on the basis of its nmr spectrum in $CDCl_3$ which showed a one-proton multiplet at 4.0–4.4 ppm for the carbinol hydrogen, H_a. Addition of trichloroacetyl isocyanate to the solution shifted this one-proton multiplet down-

(1) (a) J. Gootjes, A. B. H. Funcke, H. M. Tersteege, and W. Th. Nauta, *Arzneim. Forsch.*, **16**, 1557 (1966); (b) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 981 (1963); (c) F. L. Bach, Jr., H. J. Brabander, and S. Kushner, *J. Amer. Chem. Soc.*, **79**, 2221 (1957); (d) F. L. Bach, Jr., S. Kushner, and J. H. Williams, *ibid.*, **77**, 6049 (1955).

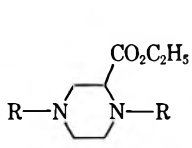
field 1.0 ppm[2] and formed a new one-proton signal at 8.96 ppm for the carbamate NH. Furthermore, conversion to the trichloroacetyl carbamate simplified the remainder of the spectrum. The four H_b protons now appeared as a doublet, J = 5 Hz, centered at 3.62 ppm, and the four H_c protons appeared as a singlet at 3.43 ppm. No change was observed in the methyl protons of the tosyl group or in the aromatic region. Additional evidence that the product contained a secondary alcohol and not a primary alcohol, as in **6**, was obtained by the appearance of the hydroxyl proton as a doublet, J = 3.5–4.0 Hz, at 5.20 ppm when the nmr was recorded in dimethyl sulfoxide.[3] That this doublet was the result of coupling of the hydroxyl proton with H_a was confirmed by its disappearance upon addition of D_2O.

The hexahydro-1*H*-1,4-diazepine **2b** was obtained by a similar reaction between the disodium salt of *N*,*N*′-ethylenebis(methanesulfonamide) (**1b**) and either 2,3-dibromo-1-propanol or 1,3-dibromo-2-propanol.

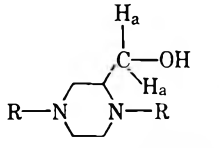
The *p*-toluenesulfonamide groups of **2a** were cleaved cleanly by phenol and hydrobromic acid[4] in acetic acid to give the acetoxy compound **3** as the dihydrobromide. Conversion of **2a** to the acetate prior to cleavage of the sulfonamide significantly increased the yield of **3**. The corresponding alcohol **4** was obtained by hydrolysis of **3** in hot water.

An authentic sample of 1,4-bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine (**6a**), mp 170.7–173.7°, was obtained by lithium aluminum hydride reduction of the ditosyl ester **5c** which was prepared in turn from the known dibenzyl ester **5a**.[5] This piperazinyl alcohol **6a**, was distinctly different from the disulfonamide obtained in the dibromopropanol reactions as determined by mixture melting point, tlc, ir, mass spectrum, and nmr. In the nmr ($CDCl_3$) spectrum of **6a**, the shielded carbinol protons, H_a, were observed as a doublet, J = 3 Hz, at 2.25 ppm. Reaction with trichloroacetyl isocyanate shifted this doublet 2.1 ppm downfield, illustrating the value of carbamate formation for the detection of carbinol protons. The 70-eV mass spectrum of **6a** showed loss of CH_2OH from the molecular ion to be a major fragmentation path. Abundant M − tosyl[6] ions were observed in the mass spectra of both **2a** and **6a**.

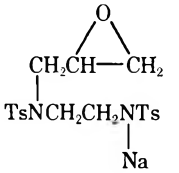
The piperazinyl alcohol **6c** was prepared by catalytic hydrogenation of **6b**[5] for comparison with the hexahydro-1*H*-1,4-diazepine alcohol **4**.



5a, R = $CH_2C_6H_5$
b, R = H
c, R = $SO_2C_6H_4CH_3$



6a, R = *p*-$CH_3C_6H_4SO_2$
b, R = $CH_2C_6H_5$
c, R = H



7

Examination of the crude products (80–85% yield) from reaction of the disodium salt of **1a** with the two isomeric dibromopropanols by tlc and nmr showed both products to be essentially identical, consisting of the hexahydrodiazepine **2a** as the major component contaminated by small amounts of the piperazine **6a** and **1a**. It was found that the crude product contained less than 10% of the piperazine **6a** by nmr comparison with an authentic mixture of **6a** and **2a**.

Formation of the same products, qualitatively, in both reactions suggests the presence of a common intermediate such as **7**. The epoxide **7** may be formed from reaction of the disodium salt of **1a** with either dibromopropanol or with epibromohydrin formed *in situ*. Ring opening of the epoxide function in **7** would occur at the preferred terminal methylene position to form the seven-membered hexahydro-1*H*-1,4-diazepine system.[7] The intermediacy of epibromohydrin in these reactions must be considered since reaction of the disodium salt of **1a** with epibromohydrin yielded the same crude product mixture as was obtained in the dibromopropanol reactions. In this experiment, the hexahydro-1*H*-1,4-diazepine **2a** was isolated in 29% yield.

Experimental Section

Nmr spectra were determined with a Varian A-60A spectrophotometer. Spectra were recorded in deuteriochloroform or trifluoracetic acid using TMS as an internal standard; those in D_2O were calibrated by the water band at 4.65 ppm. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer. Mass spectra were determined at 70 eV with a AEI-MS902 mass spectrometer. All melting points are corrected. Fluorescent silica gel G plates were used for tlc and the spots detected by uv or exposure to iodine vapor.

1,4-Bis(*p*-tolylsulfonyl)hexahydro-6-hydroxy-1*H*-1,4-diazepine (2a). Method A. From 1,3-Dibromo-2-propanol.—The sodium salt of *N*,*N*′-ethylenebis(*p*-toluenesulfonamide) was prepared by adding 50 g (0.136 mol) of the disulfonamide[8] to 600 ml of ethanol containing 0.27 mol of sodium methoxide. After being stirred at reflux for 20 min to ensure complete formation of the disodium salt, the solution was cooled to room temperature, 32.3 g (0.148 mol) of freshly distilled 1,3-dibromo-2-propanol[9] was added, and the reaction mixture was stirred at reflux for 24 hr. After cooling, 400 ml of water was added and the pH was adjusted to 10 with 10% sodium hydroxide solution. The crude product was removed by filtration, washed with water, and recrystallized from methanol to give 34 g (59%) of the title compound: mp 175.3–177.3°; homogeneous upon tlc (5% methanol–chloroform); nmr ($CDCl_3$) δ 2.45 (s, 6, CH_3), 3.0–3.9 (m, 9, OH, NCH_2), 4.0–4.4 (m, 1, CHO), 7.5 (q, 8, aromatic CH); mass spectrum, major fragments at *m/e* (rel intensity) 424 (3, M^+), 406 (3, M − H_2O), 393 (2, M − CH_2OH, possible impurity), 381 (10), 269 (100, M − tosyl[6]), 251 [10, M − (tosyl + H_2O)], 239 (10), 155 (36, tosyl), 114 (20, M − 2 tosyl).

Anal. Calcd for $C_{19}H_{24}N_2O_5S_2$: C, 53.75; H, 5.69; N, 6.60. Found: C, 53.97; H, 5.67; N, 6.59.

Method B. From 2,3-Dibromo-1-propanol. No. 1.—The disodium salt of *N*,*N*′-ethylenebis(*p*-toluenesulfonamide) was prepared from the bissulfonamide and sodium methoxide in methanol, isolated, and dried. The disodium salt, 45 g (0.109 mol), was added to a stirred solution of 25.5 g (0.117 mol) of 2,3-dibromo-1-propanol[9,10] and 6.12 g of potassium hydroxide in

(2) A downfield shift of 1.0–1.5 ppm has been reported for secondary alcohol carbinol protons under these conditions: I. R. Trehan, C. Monder, and A. K. Bose, *Tetrahedron Lett.*, 67 (1968); V. W. Goodlett, *Anal. Chem.*, **37**, 431 (1965).

(3) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); J. G. Traynham and G. A. Knesel, *ibid.*, **87**, 4220 (1965).

(4) D. I. Weisblat, B. J. Magerlein, and D. R. Myers, *ibid.*, **75**, 3630 (1953); H. R. Snyder and H. C. Geller, *ibid.*, **74**, 4864 (1952).

(5) E. Jucker and E. Rissi, *Helv. Chim. Acta*, **45**, 2383 (1962).

(6) *p*-Toluenesulfonyl, $C_7H_7O_2S$.

(7) Rearrangement of 2,3-dibromo-1-propanol to 1,3-disubstituted 2-propanol derivatives *via* epoxide intermediates has been proposed by W. W. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.*, **31**, 277 (1966); F. P. Doyle and J. H. C. Nayler, *Chem. Ind. (London)*, 714 (1955); and F. C. Whitmore, H. S. Mosher, D. P. Spalding, R. B. Taylor, G. W. Moersch, and W. H. Yanko, *J. Amer. Chem. Soc.*, **68**, 531 (1946).

(8) H. Stetter and E. E. Roos, *Chem. Ber.*, **87**, 566 (1954).

(9) The dibromopropanols used in these experiments were shown by nmr ($CDCl_3$) not to contain significant amounts of the isomeric dibromopropanol.

(10) M. L. Wolfrom, G. H. McFadden, and A. Chaney, *J. Org. Chem.*, **25**, 1079 (1960).

500 ml of ethanol at reflux. After stirring at reflux for an additional 4 hr, the reaction mixture was allowed to cool to room temperature overnight. The reaction mixture was then warmed to reflux, filtered, and cooled to give 25.4 g (56%) of the hexahydro-6-hydroxy-1,4-diazepine ditosylate, mp 175–177°. This product was identical with that prepared in method A from 1,3-dibromo-2-propanol as determined by mixture melting point, nmr ($CDCl_3$), and ir.

No. 2.—In another experiment, 2.2 g (0.010 mol) of 2,3-dibromo-1-propanol[9,10] in 20 ml of ethanol was added over 40 min to a stirred solution of 4.1 g (0.010 mol) of the dried disodium salt of *N*,*N*′-ethylenebis(*p*-toluenesulfonamide) in 80 ml of ethanol and 10 ml of water at reflux. After addition was complete, the mixture was stirred at reflux for 6 hr more and then overnight at room temperature. Water (500 ml) was added. The precipitated solid was removed, washed with water, and dried to give 3.4 g (80%) of crude product, mp 122–165°. The nmr of this crude product was essentially identical with the crude product (85% yield, mp 122–157°) obtained from an identical reaction of the disodium salt with 1,3-dibromo-2-propanol. Both products were shown by tlc (5% methanol–chloroform) to contain 1,4-bis(*p*-tolylsulfonyl)hexahydro-6-hydroxy-1*H*-1,4-diazepine as the major component and *N*,*N*′-ethylenebis(*p*-toluenesulfonamide) and 1,4-bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine as minor components. Recrystallization of the crude product from methanol gave 2.1 g (50%) of *N*,*N*′-ditosylhexahydro-6-hydroxy-1*H*-1,4-diazepine (2a), mp 173.7–176.7°, softens at 170°, identical with the product obtained in method A by mixture melting point and tlc.

Method C. From Epibromohydrin.—When epibromohydrin, 1.5 g (0.011 mol), was substituted for 2,3-dibromo-1-propanol in method B, No. 2, 3.35 g (79%) of crude product, mp 108–158°, was obtained which was essentially identical, tlc and nmr, with the crude product of method B, No. 2.

Recrystallization from methanol afforded 1.25 g (29%) of 2a, mp 172.7–176.7°, identical with the product obtained in method A by mixture melting point and tlc.

1,4-Bis(methylsulfonyl)hexahydro-6-hydroxy-1*H*-1,4-diazepine (2b). Method A. From 2,3-Dibromo-1-propanol.—To a solution of 2.7 g (0.050 mol) of sodium methoxide in 50 ml of methanol was added 5.0 g (0.0232 mol) of *N*,*N*′-ethylenebis(methanesulfonamide).[11] After the solution was stirred at reflux for 30 min, it was cooled, 1.3 g of potassium hydroxide was added, and the solution returned to reflux. A solution of 5.45 g (0.025 mol) of 2,3-dibromo-1-propanol[9,10] in 10 ml of methanol was added slowly to the hot reaction mixture. After addition was complete, the reaction mixture was stirred at reflux for 4 hr and then allowed to stand at room temperature for 3 days. The precipitated product was removed and recrystallized from methanol to give 1.5 g (24%) of product, mp 155.3–156.8°. An analytical sample, mp 156.8–158.8°, was obtained by further recrystallization from methanol: nmr (CF_3CO_2H) δ 3.14 (s, 6, CH_3), 3.6–3.9 (m, 8, NCH_2), 4.2–4.7 (m, 1, CHO).

Anal. Calcd for $C_7H_{16}N_2O_5S_2$: C, 30.86; H, 5.92; N, 10.28. Found: C, 30.81; H, 5.72; N, 10.26.

Method B. From 1,3-Dibromo-2-propanol.—The product, 21% yield, mp 157.0–162.0°, obtained from reaction of the disodium salt of *N*,*N*′-ethylenebis(methanesulfonamide) with 1,3-dibromo-2-propanol[9] by the above procedure was found to be identical with that obtained in method A from 2,3-dibromo-1-propanol by mixture melting point, nmr (CF_3CO_2H), and ir (KBr).

6-Acetoxyhexahydro-1*H*-1,4-diazepine Dihydrobromide (3).—A solution of 10 g (0.0236 mol) of 1,4-bis(*p*-tolylsulfonyl)hexahydro-6-hydroxy-1*H*-1,4-diazepine and 2.4 g (0.0236 mol) of acetic anhydride in 150 ml of a 30% anhydrous hydrogen bromide acetic acid solution was allowed to stir at room temperature for 30 min. An 8.9-g (0.094 mol) portion of phenol was added, and the reaction mixture was stirred at 60° for 6 hr and allowed to cool to room temperature overnight. Solvents were removed at 70° and 15–25-mm pressure to give an oil which, after trituration with ethyl ether and stirring with 100 ml of absolute ethanol, yielded 6.1 g (81%) of product, mp 222–223° dec. The decomposition point of this product has varied from 210 to 228° and is dependent upon the rate of heating and the temperature at which the sample is introduced. An analytical sample was obtained by recrystallization from methanol–ethyl acetate: nmr (CF_3CO_2H) δ 2.44 (s, 3, $CH_3C{=}O$), 4.0–4.4 (br m, 8, NCH_2), 5.8–6.0 (br m, 1, CHO), 8.0–8.9 (br m, 4, NH_2^+); nmr (D_2O) δ 2.24 (s, 3, $CH_3C{=}O$), 3.2–3.5 (m, 4, NCH_2), 3.5–3.9 (m, 4, NCH_2), 4.0–4.5 (m, 1, CHO); ir (KBr) 1735 cm^{-1} (ester C=O).

Anal. Calcd for $C_7H_{16}Br_2N_2O_2$: C, 26.27; H, 5.04; Br, 49.94; N, 8.75. Found: C, 25.96; H, 4.99; Br, 49.56; N, 8.71.

Hexahydro-6-hydroxy-1*H*-1,4-diazepine Dihydrobromide (4).—A solution of 200 mg (6.25 mmol) of 6-acetoxyhexahydro-1*H*-1,4-diazepine dihydrobromide in 10 ml of water was heated at reflux for 24 hr. After removing water under reduced pressure, the residue was recrystallized from methanol–ethyl acetate to give 150 mg (86%) of the alcohol, mp 257–261° dec, darkened at 247°. Further recrystallization from methanol–ethyl acetate gave an analytical sample, mp 259–262° dec, darkened at 252°.

Anal. Calcd for $C_5H_{12}N_2O \cdot 2HBr$: C, 21.60; H, 5.08; N, 10.08. Found: C, 21.70; H, 5.08; N, 10.11.

1,4-Bis(*p*-tolylsulfonyl)-2-carbethoxypiperazine (5c).—A mixture of 3.4 g (0.010 mol) of 2-carbethoxy-1,4-dibenzylpiperazine[6] and 1.5 g of a 5% palladium-on-carbon catalyst in 50 ml of glacial acetic acid was hydrogenated at an initial pressure of 50 psi until uptake of hydrogen was complete. After removal of catalyst by filtration through Supercel, the solution was concentrated under reduced pressure. The residue was stirred with 150 ml of ethyl ether, 75 ml of water, 3 g of potassium carbonate, and 3.8 g of *p*-toluenesulfonyl chloride at room temperature overnight. Addition of more potassium carbonate was necessary to keep the pH of the water solution above 8.0. After separating the ether layer and washing with a saturated sodium carbonate solution and water, it was dried (Na_2SO_4), filtered, and concentrated to an oil. Recrystallization from ethanol–water gave 1.2 g (26%) of product, mp 150.9–154.9°.[12]

Anal. Calcd for $C_{21}H_{26}N_2O_6S_2$: C, 54.06; H, 5.62; N, 6.01. Found: C, 53.98; H, 5.65; N, 6.11.

1,4-Bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine (6a).—A solution of 0.5 g (1.07 mmol) of 1,4-bis(*p*-tolylsulfonyl)-2-carbethoxypiperazine in 10 ml of dry tetrahydrofuran was added over 5 min to a stirred slurry of 0.15 g of lithium aluminum hydride in 5 ml of tetrahydrofuran under an atmosphere of nitrogen. The mixture was stirred at reflux for 2 hr and then at room temperature for another 2 hr. After decomposing unreacted lithium aluminum hydride with a saturated sodium potassium tartrate solution, the tetrahydrofuran solution was decanted and combined with fresh tetrahydrofuran washings of the gel. After drying (Na_2SO_4), the combined tetrahydrofuran extracts were concentrated and the residue was recrystallized from ethanol–water to give 0.3 g (66%) of the alcohol, mp 168.7–171.7°. Another recrystallization from ethanol–water gave an analytical sample: mp 170.7–173.7°; nmr ($CDCl_3$) δ 2.25 (d, 2, CH_2O, J = 3 Hz), 2.37 (s, 3, CH_3), 2.44 (s, 3, CH_3), 3.2–4.0 (m, 7, NCH), 7.1–7.7 (m, 8, aromatic CH); mass spectrum, major fragments at *m/e* (rel intensity) 424.1186 (3, M^+ calcd 424.1127), 393.0951 (76, M − CH_2OH), 269.0948 (10, M − tosyl[6]), 238.0768 [100, M − (CH_2OH + tosyl)], 155.0162 (43, tosyl). A mixture melting point with 1,4-bis(*p*-tolylsulfonyl)-hexahydro-6-hydroxy-1*H*-1,4-diazepine prepared from 2,3-dibromo-1-propanol was depressed to 144–152°. The ditosyl-2-hydroxymethylpiperazine, R_f 0.45–0.55, and the ditosylhexahydro-6-hydroxydiazepine, R_f 0.62–0.71, separated cleanly on tlc (5% methanol–chloroform).

Anal. Calcd for $C_{19}H_{24}N_2O_5S_2$: C, 53.75; H, 5.69; N, 6.60. Found: C, 53.59; H, 5.70; N, 6.58.

2-Hydroxymethylpiperazine Dihydrobromide (6c).—A mixture of 1.43 g (4.8 mmol) of 1,4-dibenzyl-2-hydroxymethylpiperazine[5] and 0.4 g of a 5% palladium-on-carbon catalyst in 25 ml of glacial acetic acid was hydrogenated at atmospheric pressure and 60° until uptake of hydrogen was complete. Catalyst was removed by filtration and the solution was concentrated under reduced pressure. The residue was treated with a 30% hydrobromic acid–acetic acid solution to precipitate the hydrobromide salt. Two recrystallizations from methanol–ethanol–ethyl ether gave an analytical sample, 0.97 g (73%), mp 189–191°, softens at 181°.

Anal. Calcd for $C_5H_{12}H_2O \cdot 2HBr$: C, 21.60; H, 5.08; N, 10.08. Found: C, 21.79; H, 5.19; N, 9.87.

Registry No.—2a, 28860-33-5; 2b, 28795-79-1; 3, 28795-80-4; 4, 28795-81-5; 5c, 2758-80-7; 6a, 14675-43-5; 6c, 28795-50-8.

(11) M. Cohen, *Ind. Eng. Chem.*, **47**, 2095 (1955).

(12) Reported mp 140–141° by a different route (see ref 1d).

Acknowledgment.—We wish to thank K. B. Streeter, Y. C. Lee, and their staff for elemental analyses, W. R. McGaughran and Donna Kessler for the infrared and nmr spectra, and R. E. Rhodes for the mass spectra.

Reaction of Trichloromethyl Keto Acids and Lactols in Sulfuric Acid[1]

ANTHONY WINSTON,* JOHN C. SHARP, AND RONALD F. BARGIBAND[2]

West Virginia University, Department of Chemistry, Morgantown, West Virginia 26506

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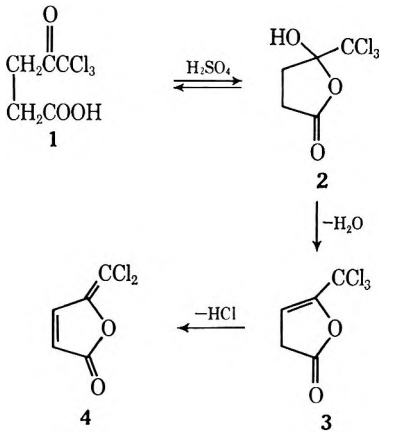
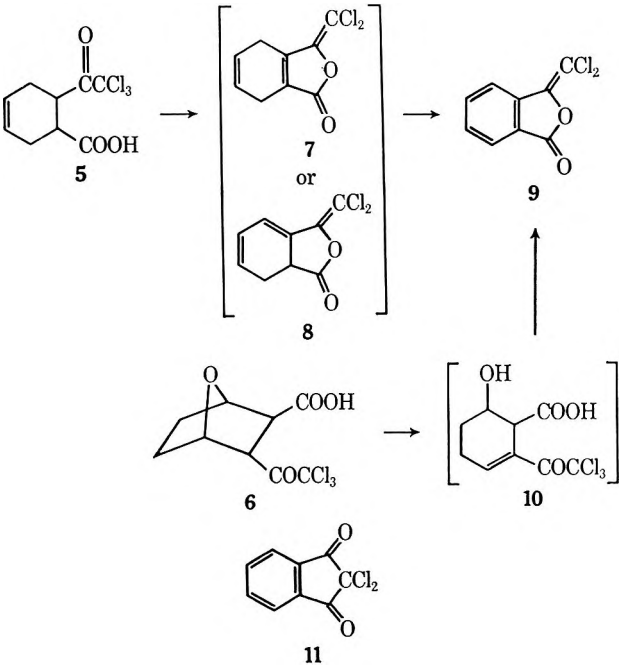
Earlier we suggested that the conversion of 5,5,5-trichlorolevulinic acid (**1**) to 5,5-dichloro-4-hydroxy-2,4-pentadienoic acid lactone (5,5-dichloroprotoanemonin) (**4**) in concentrated sulfuric acid proceeded by way of an initial cyclization to the lactol tautomer **2** followed in turn by a dehydration to **3** and a 1,4-conjugate elimination of hydrogen chloride to give **4** (Scheme I).[3]

SCHEME I



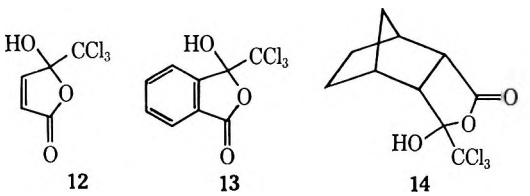
Although under normal conditions the open chain structure **1** is favored over the cyclic structure 2,[4] protonation of the trichloroacetyl carbonyl group in the acid media would promote cyclization. To provide additional insight as to the course of this reaction and, at the same time, to explore the possibility of using this means as a general method for synthesizing halogen derivatives of protoanemonin, reactions of a variety of trichloromethyl keto acids or their cyclic lactol tautomers with concentrated sulfuric acid were examined.

Reaction of keto acid **5** was expected to give lactone **7** or **8**, but the evidence is clear that the aromatic structure **9** is formed. The analytical data reveal only four protons. The complex unsymmetrical multiplet centered at τ 2.2 in the nmr spectrum is consistent with an ABCD pattern of a unsymmetrical ortho disubstituted benzene. Infrared bands at 1795 (lactone C=O) and 1650 cm^{-1} (C=CCl$_2$) commonly occur in the spectra of protoanemonin derivatives.[3,5] As an alternate possibility, 2,2-dichloro-1,3-indandione (**11**), first reported by Zincke[6] in 1888, not only has a melting point of 124–125°, some 18° higher than ours, but is clearly inconsistent with the spectral data.



Reaction of *trans*-keto acid **6** also gave the aromatic dichloroprotoanemonin analog **9**, probably through an initial ring opening to keto acid **10**. Dehydration of **10** would bring the carbonyl and trichloroacetyl groups into coplanarity, which would favor cyclization to the lactol tautomer. A second dehydration and a dehydrohalogenation would lead to product **9**.

Lactols **12**, **13**, and **14** failed to react with concentrated sulfuric acid at room temperature even after prolonged reaction times and only starting materials were isolated. In accordance with the suggested mechanism (Scheme I), the failure of lactols **12** and **13** to react is consistent with the lack of appropriately placed hydrogens to provide for the dehydration and dehydrohalogenation steps. However, the stability of lactol **14** under these conditions must be due to other causes, since the required hydrogens are indeed present. We suggest that this stability is a direct result of the considerable strain energy involved in the ring distortion which would accompany a dehydration.



Unsaturated bicyclic lactol **15** failed to react normally with sulfuric acid to give an analog of dichloroprotoanemonin. However, a reaction did occur to give tetracyclic lactone **16**, the structure of which was consistent with the analytical data, spectral data, and

(1) From the Ph.D. dissertations of J. C. Sharp (1966) and R. F. Bargiband (1970).

(2) NASA Trainee, 1967–1970.

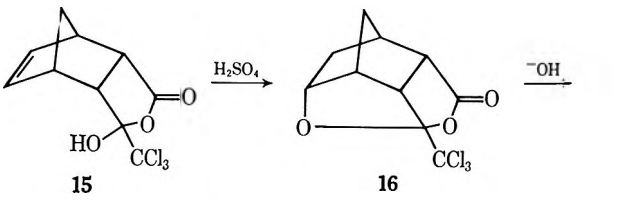
(3) A. Winston and J. C. Sharp, *J. Amer. Chem. Soc.*, **88**, 4196 (1966).

(4) A. Winston, J. P. M. Bederka, W. G. Isner, P. C. Juliano, and J. C. Sharp, *J. Org. Chem.*, **30**, 2784 (1965).

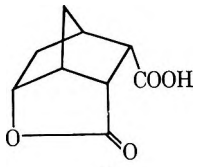
(5) A. Winston and R. N. Kemper, *Tetrahedron*, **27**, 543 (1971).

(6) T. Zincke, *Ber.*, **21**, 491 (1888).

the failure of the compound to react with bromine or to undergo catalytic hydrogenation. Confirmation of the structure was obtained by converting **16** to the known acid lactone **17**[7] by aqueous base.



15 **16**



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Although it has long been felt that for structure **15** the smaller hydroxyl rather than the trichloromethyl group would be directed under the bicyclic ring as shown, the ease of cyclization of **15** and **16** confirms the close proximity of the hydroxyl to the ring double bond.

The reaction of **15** with sulfuric acid is striking in that the solution takes on a beautiful deep blue color (see Experimental Section for details). This effect is not observed for any of the other compounds, even the closely related compound **14**, nor is color produced on dissolution of the product **16** in sulfuric acid. The origin of the blue color has not been confirmed, but initial results indicate that this effect is not really associated with the primary sequence of **15** and **16**. Inhibition of color formation by addition of small amounts of sodium azide as well as the appearance of an esr signal suggests that a radical is involved.

The results of this study support the proposed mechanism outlined in Scheme I for the conversion of trichloromethyl keto acids and lactols to 5,5-dichloroprotoanemonin analogs and are consistent with the requirements for hydrogen at C-2 and C-3. The synthetic utility of the reaction is, however, limited by unfavorable steric strain and competing side reactions inherent in concentrated sulfuric acid.

Experimental Section

The trichloromethyl keto acids and lactols were prepared as described in previous communications.[4,8] The 100% sulfuric acid was prepared by mixing appropriate amounts of 96.86% acid with fuming sulfuric acid. Melting points are uncorrected. Analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. The ir and nmr spectra were obtained using Perkin-Elmer Model 137 and Varian Associates HA-60 instruments, respectively. Protoanemonin and 5,5-dichloroprotoanemonin are powerful vesicants and handling compounds of this type should be carried out with considerable care.[3]

General Procedure for Sulfuric Acid Reactions.—The trichloromethyl lactol or keto acid was dissolved in 100% sulfuric acid at room temperature and allowed to stand with intermittant stirring. The solution was poured over ice and the products were isolated by filtration or extraction into ether. The solid products were purified by crystallization or sublimation and characterized. The experimental details, the products isolated, and the yields of purified products are reported in Table I.

Table I

Reaction of Lactols and Keto Acids with Concentrated Sulfuric Acid

Reactant	Wt, g	Reaction time, days	Compd isolated	Wt, g	Yield, %
5	0.10	9	**9**	0.06	70
6	0.20	2	**9**	0.10	70
12	0.30	17	**12**	0.05	17
13	0.30	34	**13**	0.27	90
14	0.30	7	**14**	Trace	
15	20.0	1 hr	**16**	14.8	74

2-(2,2-Dichloro-1-hydroxyvinyl)benzoic Acid Lactone (9).—Reaction of either *cis*-2-trichloroacetyl-4-cyclohexenecarboxylic acid (**5**) or *endo*-3-trichloroacetyl-7-oxabicyclo[2.2.1]heptane-*exo*-2-carboxylic acid (**6**) with concentrated sulfuric acid produced identical products as shown by comparison of their ir and nmr spectra. The solid was purified by sublimation to give white crystals of **9**: mp 107°; ir (Nujol) 1795 (C=O) and 1650 cm^{-1} (C=CCl_2);[5] nmr ($CDCl_3$) τ 2.2 unsymmetrical multiplet (arom H).

Anal. Calcd for $C_9H_4Cl_2O_2$: C, 50.20; H, 1.86; Cl, 33.00. Found: C, 50.06; H, 1.91; Cl, 32.83.

Reaction of 4,4-Dihydroxy-5,5,5-trichloro-2-pentenoic Acid Lactone (12), 3-Hydroxy-3-trichloromethylphthalide (13), and *endo-cis*-3-Trichloroacetylbicyclo[2.2.1]heptane-2-carboxylic Acid Lactol (14) with Sulfuric Acid.—The solids isolated were identified by their ir spectra as consisting entirely of the starting material.

5-Trichloromethyl-4,11-dioxatetracyclo[5.2.1.$1^{5,8}$.$0^{2,6}$]undecan-3-one (16).—Since this reaction was carried out somewhat differently from the others, a full description will be given. To 20.0 g (0.071 mol) of *endo-cis*-3-trichloroacetylbicyclo[2.2.1]-4-heptene-2-carboxylic acid lactol (**15**) was added 200 ml of concentrated sulfuric acid over a 15-min period with stirring. A very deep blue color appeared immediately, and the reaction was slightly exothermic. After all of the solid had dissolved, the flask was immersed in an ice–water bath and 600 ml of water was slowly added, whereupon a black solid was gradually formed. The solid was collected, washed well with water, and dried *in vacuo* at 60° for 4 hr, yielding 18.3 g of a black powder. Thin layer chromatography of the solid, using 100% ether, 70:30 ether–chloroform, or 60:40 ether–acetone as eluents showed only one migrating component. The solid was extracted with chloroform, the chloroform solution was treated with decolorizing charcoal, and the solvent was removed *in vacuo* at 50–60°, leaving a yellow oil, which rapidly crystallized upon cooling. Recrystallization from carbon tetrachloride–hexane gave 14.8 g (0.052 mol, 73.2%) of white crystals of lactone **16**, mp 149.5°, ir (KBr) 1795 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_9Cl_3O_3$: C, 42.36; H, 3.20; Cl, 37.52. Found: C, 42.50; H, 3.29; Cl, 37.29.

When this reaction was carried out in the presence of sodium azide, the same product, lactone **16**, was isolated but no blue color intermediate was observed. On dissolving lactone **16** in sulfuric acid, no blue color was observed nor was the blue color produced in any of the other sulfuric acid reactions. An esr spectrum of the blue sulfuric acid solution revealed a complex pattern centered at 3345 G and extending over a range of about 40 G. This signal faded after several days although the blue color remained essentially unaffected. When additional lactone **16** was added, the esr signal returned.

***endo-cis*-5-Hydroxybicyclo[2.2.1]heptane-2,3-decarboxylic Acid Lactone (17).**—A mixture of 7.0 g (35 mmol) of lactone **16** and 60 ml of 5% aqueous sodium hydroxide was heated under reflux for 4.5 hr. Acidification of the reaction mixture, evaporation of the water to dryness, and extraction of the resulting solid with ether yielded 5.46 g (30 mmol, 85%) of a tan solid. Sublimation afforded white crystals of **17**: mp 200–201° (lit.[7] mp 200–201°); ir (KBr) 1770 (lactone C=O) and 1692 cm^{-1} (acid C=O). The infrared spectrum was identical with that of an authentic sample of lactone acid **17** prepared by the method of Koch, *et al.*[7]

Registry No.—**5**, 2903-44-8; **6**, 28795-85-9; **9**, 28795-86-0; **15**, 28795-87-1; **16**, 28795-88-2.

(7) H. Koch, J. Kotlan, and H. Markut, *Monatsh. Chem.*, **96**, 1646 (1965).
(8) A. Winston, J. C. Sharp, K. E. Atkins, and D. E. Battin, *J. Org. Chem.*, **32**, 2166 (1967).

The Preparation of sec-Alkyl Perchlorates in Strong Acid

DAVID M. HOFFMAN

Corporate Research Department, Sun Oil Company, Marcus Hook, Pennsylvania 19061

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Covalent esters of perchloric acid have been briefly mentioned in the literature.[1] The lower molecular weight alkyl perchlorates are rather unstable compounds, and preparation of the neat liquids can be quite hazardous.[1] Although some workers have actually distilled them,[1b,2] others have avoided their isolation and used them as formed *in situ*.[3] The most common preparation of alkyl perchlorates is the reaction of an alkyl iodide with silver perchlorate.[1] The

$$RI + AgClO_4 \xrightarrow{\text{solvent}} RClO_4 + AgI$$

reaction of anhydrous perchloric acid with alcohols or olefins is quite hazardous but has been reported,[4,5] and a small amount of perchlorate ester was isolated from the reaction of 9-octadecene or 9-octadecanol with 70% perchloric acid at 100° for 3 hr.[6]

We have developed a new and facile preparation of secondary alkyl perchlorates which does not require use of expensive silver perchlorate or alkyl iodides. The new procedure involves addition of a secondary alcohol or unbranched olefin to a well-stirred emulsion of perchloric acid, sulfuric acid, and an inert hydrocarbon or halocarbon. The acid reagent can be prepared by combining 70% perchloric acid, 96% sulfuric acid, and oleum, or by dissolving lithium perchlorate in 96% sulfuric acid. The formation of isomeric secondary alkyl perchlorates is, in most cases, very rapid and virtually quantitative. The ester products are found in the organic layer, from which they may be isolated (*with caution*) if desired. The composition of the isomeric mixture is dependent on the reaction conditions and can often be made to highly favor one specific isomer.

The key to the synthesis is the use of the nonreactive organic phase in combination with the perchloric acid–sulfuric acid reaction medium. Upon addition to such a system both secondary alcohols and unbranched olefins react rapidly to give either alkyl hydrogen sulfate or alkyl perchlorate. The alkyl perchlorate, being covalent in nature, moves quickly to the organic layer where it is largely protected from further decomposition. The alkyl hydrogen sulfate remains in the acid layer until further reaction produces alkyl perchlorate. However, prolonged maintenance of the emulsion, particularly at room temperature or above, leads to a slow decomposition of the perchlorate, giving products which are typical of those obtained from long exposure of alcohols or olefins to sulfuric acid.[7]

The conditions necessary for the best results are typical of reactions carried out in concentrated sulfuric acid. For maximum yield and minimum isomerization it is advantageous to maintain the reaction temperature just above the freezing point of the emulsion (about 15°). This is particularly true for compounds of composition C_{10} or less (except for isopropyl alcohol, *vide infra*). For optimum yield the acid strength should be kept between 94 and 96 wt % combined acids. With less than 90% acid incomplete reaction occurs and with 100% acid a rather rapid decomposition of perchlorate takes place. An excess of perchloric acid over olefin or alcohol and a large amount of inert organic layer also serve to increase yields. Table I gives typical product yields at two reaction temperatures.

TABLE I
YIELD OF SECONDARY ALKYL PERCHLORATES

Perchlorate precursor	Alkyl perchlorate yield (%)[a] −10°	25°
Propene	96	*b*
1-Pentene	98	*b*
1-Hexene	99	9
Cyclohexene	89	14
3-Heptene	84	27
1-Decene	100	91
1-Octadecene	100	100
4-Phenyl-1-butene	85	35
5-Methyl-1-hexene	78	*b*
1,7-Octadiene[c]	85	*b*
2-Propanol	6	65
2-Butanol	88	<5
3-Hexanol	98	10
Diisopropyl sulfate[d]	99	*b*

[a] See Experimental Section; the products are often mixtures of *sec*-alkyl perchlorates, the composition of which depends on the conditions of the reaction. [b] Yield not determined. [c] Yield based on both double bonds reacting. [d] Yield based on both isopropyl groups reacting.

Due to the hazardous nature of the perchlorate products, they were not actually isolated and analyzed in pure form, but their presence was established by several observations. First, the hydrocarbon layer of the reaction forms a pyridine–copper nitrate–perchlorate complex in direct proportion to the amount of olefin or alcohol added to the reaction.[8] Careful removal of the solvent from the reaction product of 2-heptene produced an oil which was insoluble in water and heavier than water (the densities are greater than one for perchlorate esters of C_8 or less[2]). When a small portion of the hydrocarbon layer was placed on a preheated hot plate, a small explosion occurred after evaporation of the solvent. Lastly, the nmr spectra in chlorobenzene are completely consistent with those expected for secondary alkyl perchlorates, for example 2-hexylperchlorate [nmr (PhCl) τ 9.23 (t, 3), 8.78 (d, 3), 8.60 (m, 6), 5.20 (m, 1)] and 2-propyl perchlorate [nmr (PhCl) τ 8.88 (d, 6), 5.05 (m, 1)].

The formation of isomeric mixtures of perchlorates, when permitted by the structure of the reacting molecule, needs some further comment. For this purpose the *sec*-hexyl system serves as an excellent model. Table II contains the isomeric distribution of *sec*-hexyl perchlorates using various hexyl precursors under dif-

(1) For brief reviews, see (a) H. Burton and P. F. G. Praill, *Analyst (London)*, **80**, 4 (1955); (b) R. D. Stewart, "Perchlorates," J. C. Schumacker, Ed., Reinhold, New York, N. Y., 1960, pp 67, 214.

(2) J. Radell, J. W. Connolly, and A. J. Raymond, *J. Amer. Chem. Soc.*, **83**, 3958 (1961).

(3) H. Buron, D. A. Munday, and P. F. G. Praill, *J. Chem. Soc.*, 3933 (1956).

(4) J. Meyer and W. Spormann, *Z. Anorg. Allg. Chem.*, **228**, 341 (1936).

(5) S. J. Tauber and A. M. Eastham, *J. Amer. Chem. Soc.*, **82**, 4888 (1960).

(6) J. S. Showell and I. S. Shepherd, *J. Org. Chem.*, **34**, 1097 (1969).

(7) N. C. Deno, *Chem. Eng. News*, 88 (Oct 5, 1964).

(8) W. Bodenheimer and H. Weiler, *Bull. Res. Counc. Isr.*, **4**, 316 (1954); *Chem. Abstr.*, **49**, 13022*i* (1955).

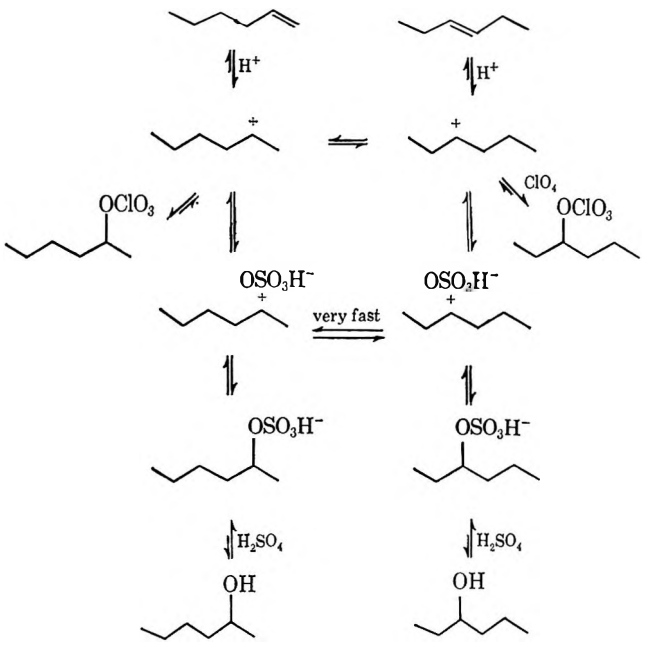
TABLE II
ISOMER DISTRIBUTION OF 2- AND 3-HEXYL PERCHLORATES AT −15°

Reactant	Isomer distribution (%) 2-isomer	3-isomer
1-Hexene	80	20
2-Hexene	45	55
3-Hexene	20	80
2-Hexanol	57	43
3-Hexanol	57	43
1-Hexene[a]	50	50
3-Hexene[a]	50	50

[a] Perchloric acid was added immediately after the olefin was added to a sulfuric acid–chlorobenzene emulsion.

ferent conditions. The reactions were carried out using chlorobenzene as the organic layer, and the isomer distributions were determined by comparing the nmr spectra with spectra of known mixtures of the corresponding hexyl benzoates. Both 2-hexanol and 3-hexanol give the same mixture of hexyl perchlorates regardless of the reaction conditions. In contrast, the hexenes produce isomeric mixtures of perchlorates which are dependent on the olefin used as well as on the reaction conditions. Thus, the addition of olefin to the perchloric acid–sulfuric acid–chlorobenzene emulsion at the lowest temperature possible (−15°) gives mostly the product formed by addition of perchloric acid across the double bond. Higher reaction temperatures or addition of the olefin to a sulfuric acid–chlorobenzene emulsion prior to the addition of perchloric acid produced a mixture of isomers similar to that obtained from the alcohols. Scheme I summarizes the various equilibria which lead to these different product distributions.

SCHEME I



There are at least two different pathways leading to perchlorates, one by direct addition across a double bond and the other proceeding through the alkyl hydrogen sulfate. The former route is open only to olefins, whereas both alcohols and olefins (under certain conditions) can react *via* the second pathway. Secondary alcohols react rapidly with 96% sulfuric acid to give the alkyl hydrogen sulfate.[9] The results obtained using 2-propanol (*vide infra*) indicate that the reaction with sulfuric acid occurs in preference to a direct reaction of the alcohol with perchloric acid. The alkyl hydrogen sulfate, once formed, reacts further with perchloric acid to give perchlorate ester at a rather rapid rate. During this sequence of reactions an equilibrium mixture of *sec*-alkyl perchlorates is formed, probably resulting from rapid equilibration through ion pair intermediates. Since the individual perchlorate isomers formed *via* olefins are rather stable toward isomerization in this system, the equilibration must occur prior to the final perchlorate formation. As indicated, olefins can add perchloric acid directly across the double bond without formation of alkyl hydrogen sulfate. Apparently, perchloric acid (or perchlorate ion) can compete very well with sulfuric acid (or bisulfate ion) for the carbonium ion formed on protonation of the olefin. If, however, the olefin is allowed to form the alkyl hydrogen sulfate before the addition of perchloric acid, the resulting product is a mixture of perchlorate isomers, just as from alcohols.

The behavior of 2-propanol requires further comment. It differs from other secondary alcohols in that at low temperature little or no perchlorate ester is formed, whereas at room temperature the yield of perchlorate is considerably greater than it is with the C_4 to C_8 secondary alcohols. The lack of reactivity at low temperatures can be shown to be due to the extremely slow formation of 2-propyl hydrogen sulfate, which can be demonstrated by the nmr spectrum of 2-propanol added to 96% sulfuric acid at −10°. The spectrum contains a methyl doublet due to equilibration between 2-propanol and its conjugate acid. Warming to 0–5° causes a slow change in the spectrum to the methyl doublet of 2-propyl hydrogen sulfate which is located 0.087 ppm upfield of the original doublet. Diisopropyl sulfate reacts rapidly at −10° in the perchloric acid–sulfuric acid system to produce 2-propyl perchlorate quantitatively, demonstrating further that the slow step must be the original esterification of the 2-propanol. The formation of perchlorate ester from 2-propanol at room temperature is due not only to the more rapid rate of formation of 2-propyl hydrogen sulfate but also to the greater stability of the 2-propyl group toward the acid layer, which permits it to survive at this temperature.

The formation of alkyl perchlorates from branched alcohols and olefins has met with only limited success due to the instability of the resulting *tert*-alkyl perchlorate products under the reaction conditions. Primary alcohols react very slowly and apparently give some perchlorate but only after isomerization to secondary structures.

Experimental Section

Preparation of Perchlorate Esters.—Anhydrous lithium perchlorate (3.5 g, 33 mmol) dissolved in 35 ml of 96% H_2SO_4 was added to a 100-ml Morton flask equipped with an overhead stirrer and ice condenser, and cooled in an ice–salt bath. To this was added 15.0 cc of hexane; the contents were emulsified by stirring at 1500 rpm. The reactant olefin or alcohol (1.0 ml, 5–8 mmol) was added by syringe pump over 6 min and the contents of the flask were stirred for an additional 2–10 min. The emulsion was allowed to break and the flask warmed to room tem-

(9) R. J. Gillespie and J. A. Leisten, *Quart. Rev., Chem. Soc.*, **8**, 40 (1954), and references therein.

perature. Samples of the hydrocarbon layer were then examined for perchlorate content by the colorimetric method described below.

The $LiClO_4$ served only as a source of $HClO_4$ and could be replaced by any inorganic perchlorate which would dissolve sufficiently in H_2SO_4 to liberate the required perchloric acid. Alternatively 70% $HClO_4$ could be added directly to 96% H_2SO_4. If a large amount of perchloric acid was used, it was necessary to add oleum to compensate for the water in the 70% $HClO_4$. The hexane could be replaced with a variety of other substances providing they did not react with H_2SO_4 and the alkyl perchlorate was soluble in them.

Due to the explosive nature of the compounds prepared, the reaction vessel was shielded and isolation of the perchlorate esters was avoided. As long as solvent was present the esters were apparently quite stable. However, if a drop of the hydrocarbon solution was placed on a hot plate, a bright flash was observed after the evaporation of the solvent, illustrating the highly explosive nature of these compounds.

Determination of Perchlorate Esters.—The amount of perchlorate ester present in the hydrocarbon phase of the reaction was estimated by a colorimetric method similar to that described by Bodenheimer and Weiler.[3] A standard solution of the copper nitrate–pyridine complex was prepared by combining 4.8 g of $Cu(NO_3)_2 \cdot 3H_2O$, 50 ml of H_2O, and 11 ml of pyridine and diluting to 1 l. with ethanol. Reference standards were prepared from a titrated solution of 70% $HClO_4$ in EtOH, EtOH, hexane, and the standard solution such that the final solutions contained 5.0 ml of standard, 1.0 ml of EtOH, and 2.0 ml of hexane. The amount of perchlorate formed in a reaction was determined by combining 5.0 ml of standard, 1.0 ml of EtOH, and varying quantities of the hexane layer from the reaction. Additional hexane was added such that the total amount of hexane was 2.0 ml and the tubes were allowed to stand for 1 hr. After centrifuging, the color was compared to the reference tubes. The amount of perchlorate found was then extrapolated to the entire hexane layer. By making 4–6 determinations using different quantities of the hexane layer, an accuracy of ±3% was achieved.

Determination of Nmr Spectra of Alkyl Perchlorates.—The nmr spectra were determined on either a Varian A-60 or T-60 spectrometer. For this purpose the alkyl perchlorates were prepared as described above with the exception that chlorobenzene or hexafluorobenzene was substituted for the hexane layer. The concentration of the perchlorates was 10–20% in the solvent and TMS was used as an internal standard.

On several occasions the nmr was used to estimate the yield of alkyl perchlorate. A weighed portion of toluene was used as the internal standard and combined with a portion of the chlorobenzene layer containing the alkyl perchlorate. The amount of perchlorate was then extrapolated to the entire chlorobenzene layer. This analysis was in very close agreement (±2%) with the one obtained by the colorimetric method.

Registry No.—Perchloric acid, 7601-90-3.

Acknowledgment.—The author wishes to thank Mr. H. Smith Sipple and Mr. Herbert C. Williamson for technical and analytical assistance and Professor Wayland E. Noland for helpful discussions of this work.

Reactions of 2,6-Cycloheptadienone and 2,7-Cyclooctadienone with Primary and Secondary Amines. Synthesis of Tropinones and Pseudopelletierines

A. T. Bottini* and J. Gal

Department of Chemistry, University of California, Davis, California 95616

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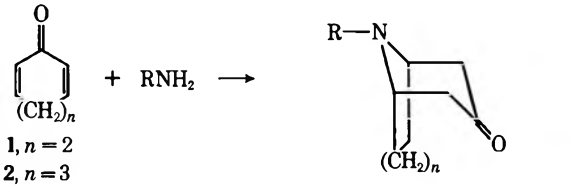
In his paper describing the synthesis of tropinone (**3a**) by condensation of methylamine with succindialdehyde and acetonedicarboxylic acid, Robinson[1] also noted "that tropinone might result...by the addition of methylamine to a cycloheptadienone...." Nearly 10 years ago, Horák[2] reported the characterization by paper chromatography of tropinone prepared from a large excess of methylamine and 20 mg of a mixture of cycloheptadienones, which had been prepared by treatment of a tropinonium salt with base.[3] In 1965, Garbisch[4] described the preparation of 2,6-cycloheptadienone (**1**), 2,7-cyclooctadienone (**2**), and other cycloalkadienones from their corresponding cycloalkanones. Although four steps are required in Garbisch's synthesis, they are described thoroughly and the overall yields are good. The reasonable accessibility of **1** and **2** made it possible for us to check and extend the alternative synthetic route suggested by Robinson, and we describe here an easily accomplished synthesis of tropinone (**3a**), pseudopelletierine (**4a**), and several of their N-substituted homologs.[5]

Addition of 1 equiv of 2,6-cycloheptadienone[4] (**1**) to a 2 *M* solution of methanolic methylamine at room temperature resulted in a mildly exothermic reaction that could be followed conveniently by examination of the vinyl region in the nmr spectrum. Within 30 min, >95% of the dienone had reacted, and evaporation of the solvent left crude tropinone (**3a**). Use of 2,7-cyclooctadienone[4] (**2**) in place of **1** resulted in a more rapid reaction leading to pseudopelletierine (**4a**).[6] We have also used this method to prepare *N*-benzyl- and *N*-ethylnortropinone (**3b** and **3c**) and *N*-benzylnorpseudopelletierine (**4b**).



1, $n = 2$
2, $n = 3$

3, $n = 2$ **a**, R = CH_3
4, $n = 3$ **b**, R = $PhCH_2$
c, R = C_2H_5

In addition, we have found that the cycloalkadienones **1** and **2** react rapidly (10 and 1 min, respectively) with equivalent amounts of dimethylamine hydrochloride (2 *M* in methanol) in the presence of dimethylamine (*ca.* 0.1 *M*) to give the methochlorides of **3a** and **4a** (**5** and **6**) directly.[8]

Yields of purified products and their melting or boiling points are summarized in Table I.

Preparation of tropinone, pseudopelletierine, and their N-substituted homologs by condensation of a

(1) R. Robinson, *J. Chem. Soc.*, **111**, 762 (1917).

(2) V. Horák and P. Zuman, *Tetrahedron Lett.*, 746 (1961); V. Horák, *Collect. Czech. Chem. Commun.*, **28**, 1614 (1963).

(3) J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *J. Amer. Chem. Soc.*, **77**, 4401 (1965).

(4) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965). *Caution!* **1** and **2** are skin irritants.

(5) A related condensation has been described by C. Grundmann and G. Ottman [*Justus Liebigs Ann. Chem.*, **605**, 24 (1957)], who prepared anhydroecgonine by condensing methylamine at 125° with the isomeric cycloheptatrienecarboxylic acids obtained by the Buchner reaction.

(6) The cyclooctadienone obtained by oxidation of 1,5-cyclooctadiene[7] might also be suitable for this and related preparations.

(7) W. J. Farrissey, Jr., U. S. Patent 3,287,427 (Nov 22, 1966); *Chem. Abstr.*, **66**, P115361y (1967).

(8) For other examples of formation of a bicylic system by Michael-type addition of a tertiary amine, see L. A. Paquette and L. D. Wise, *J. Amer. Chem. Soc.*, **87**, 1561 (1965).

TABLE I

PRODUCTS FROM CONDENSATIONS OF 2,6-CYCLOHEPTADIENONE OR 2,7-CYCLOOCTADIENONE WITH PRIMARY AMINES AND DIMETHYLAMINE HYDROCHLORIDE

Compd	Yield, % (wt, g)[a]	Mp or bp (mm), °C
3a	64 (0.89)	42.5–44 (dist),[b] 97 (12)
3b	59 (3.2)	23–24 (dist), 123–124 (0.18)[c]
3c	56 (1.7)	48 (0.1)[d]
4a	53 (0.65)	62–64 (subl)[e]
4b	62 (1.70)	72–73 (MeOH–H_2O)[f]
5	64 (1.2)	213 dec (MeOH–Et_2O)[g]
6	78 (0.79)	268 dec (MeOH–Et_2O)[h]

[a] Results tabulated here were from the first effort. Purified products were also characterized by means of their ir and nmr spectra. [b] Mmp 42.5–44°. [c] $n^{24}D$ 1.5540 [lit.[11a] bp 134–137° (0.4 mm), $n^{25}D$ 1.5526]. Dipiperonylidene derivative, mp 194–195° (C_2H_5OAc) (lit.[11b] mp 194–195°). [d] $n^{24}D$ 1.4892 [lit.[11c] bp 41–42° (0.08 mm), $n^{20}D$ 1.4885]. Picrate, mp 190–191° (H_2O) (lit.[11c] mp 189°). [e] Lit.[10b] mp 62–64°. [f] Lit.[11d] mp 70–73° (employing petroleum ether). [g] *Anal.* Calcd for $C_9H_{16}NOCl$: C, 56.98; H, 8.45; N, 7.38. Found: C, 57.00; H, 8.45; N, 7.35. [h] *Anal.* Calcd for $C_{10}H_{18}NOCl$: C, 58.96; H, 8.90; N, 6.87. Found: C, 58.88; H, 8.94; N, 6.61.

primary amine with the appropriate cycloalkadienone appears to be the most attractive alternative[9] to the versatile and well-tested Robinson–Schöpf synthesis.[1,10,11]

Registry No.—**1**, 1192-93-4; **2**, 1073-76-3; **3a**, 532-24-1; **3b**, 28957-72-4; **3c**, 3423-30-1; **4a**, 28861-13-4; **4b**, 28861-14-5; **5**, 28861-15-6; **6**, 28957-73-5.

Acknowledgment.—We wish to thank Professor E. C. Friedrich for a generous sample of **2**.

(9) For other alternatives, see P. Karrer and H. Alagil, *Helv. Chim. Acta*, **30**, 1776 (1947); B. F. Putney and T. O. Soine, *J. Amer. Pharm. Ass.*, **44**, 17 (1955); W. Parker, R. A. Raphael, and D. I. Wilkinson, *J. Chem. Soc.*, 2433 (1959); N. J. Turro and S. S. Edelson, *J. Amer. Chem. Soc.*, **90**, 4499 (1968).

(10) (a) C. Schöpf and G. Lehmann, *Justus Liebigs Ann. Chem.*, **518**, 1 (1935); (b) A. C. Cope, H. L. Dryden, Jr., and C. F. Howell, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 816.

(11) Papers in which applications of the Robinson–Schöpf synthesis are described include (a) S. Archer, U. S. Patent 2,845,427 (July 29, 1958) [*Chem. Abstr.*, **53**, 430 (1959)]; (b) L. C. Keagle and W. H. Hartung, *J. Amer. Chem. Soc.*, **69**, 1608 (1946); (c) K. Nador, Gy. Hajdu, B. Szecso, and F. Zima, *Arzneim.-Forsch.*, **12**, 305 (1962); (d) C. F. Boehringer and Soehne GmbH, Netherland Appl. 284,570 (Jan 25, 1965); *Chem. Abstr.*, **63**, 4354 (1965).

Geometrical Isomers of Ortho-Substituted Acetophenone *N,N*-Dimethylhydrazones

GEORGE R. NEWKOME*[1] AND N. S. BHACCA

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

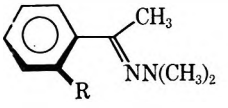
Received September 22, 1970

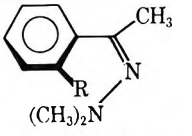
Our previous paper[2] described the preparation of aldehyde and ketone *N,N*-dimethylhydrazones and their facile conversion to the corresponding azine-free unsubstituted hydrazones. We now wish to report the presence of *E* and *Z* ortho-substituted acetophenone *N,N*-dimethylhydrazones[3] and the isolation of their methiodides. During the course of this work, 16 meta- and para-substituted acetophenone *N,N*-dimethylhydrazones were prepared[2] and in each case existed as a single stereoisomer, which was presumed to have the *E* configuration through the analysis of the nmr spectral data. The CCH_3 chemical shifts varied randomly from 2.24 to 2.35 ppm downfield from TMS, whereas the NCH_3 chemical shifts changed from 2.49 to 2.62 ppm correlating rather well to the Hammett $\sigma_{m,p}$ parameters,[4] albeit the chemical shift differences are quite small. Similar preponderance of a single isomer has been reported for ketone *N*-methyl imines[5] and aldehyde *N,N*-dimethylhydrazones.[6]

The nmr spectra of the ortho-substituted acetophenone *N,N*-dimethylhydrazones (**1a–d**)[2] no longer appeared as two characteristic methyl singlets but rather indicated a mixture of two geometric isomers or conceivably restricted rotational isomers. The observed resonances have been attributed to mixtures of *E* and *Z* isomers, since the latter was eliminated by absence of any simplification of the nmr spectra at elevated temperatures.[7] The glc analysis[8] of **1a** showed a 60:40 ratio of the isomeric dimethylhydrazones; attempted preparative glc collection of each isomer in our hands resulted in the isolation of fractions which isomerized to mixtures identical with the starting material as attested to by both nmr and glc analysis. Similar results were obtained with **1** irrespective of the ortho substituent (Table I). The rapid syn–anti isomerization of **1a–d** can occur *via* either the in-the-plane inversion mechanism or out-of-plane rotation mechanism; the inversion mechanism seems to have been conclusively verified in

TABLE I

PMR CHEMICAL SHIFTS[a] FOR METHYL PROTONS





		E isomer		Isomer	*Z* isomer	
Compd	R	C–CH_3	N–CH_3	ratio, *E*:*Z*	C–CH_3	N–CH_3
1a	OCH_3	2.25	2.51	60:40	2.10	2.28
1b	CH_3	2.31	2.50	53:47	2.08	2.28
1c	Br	2.24	2.52	57:43[b]	2.15	2.31
1d	Cl	2.28	2.51	68:32[b]	2.15	2.25
1e	H	2.26	2.52	100:0		

[a] Chemical shifts are parts per million downfield from internal TMS; CCl_4 solvent, concentration 7%. [b] Estimated by nmr data.

(1) To whom correspondence should be addressed.

(2) G. R. Newkome and D. L. Fishel, *J. Org. Chem.*, **31**, 677 (1966); *Org. Syn.*, **50**, 102 (1970).

(3) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968); reviewed by E. L. Eliel, *J. Chem. Educ.*, **48**, 163 (1971).

(4) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, pp 85–93.

(5) J. B. Lambert, W. L. Oliver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 5085 (1965).

(6) (a) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *Tetrahedron Lett.*, 1081 (1964); (b) G. J. Karabatsos and R. S. Taller, *Tetrahedron*, **24**, 3923 (1968).

(7) Samples were subjected to temperatures of as high as 180°; the nmr spectra were essentially unaltered over the range −80 to 180°. The distribution ratio at both 30 and 180° corresponded well to the glc ratio of isomers.

(8) A 0.5 in × 9 ft stainless steel column packed with 20% SE-30 on 60–80 Chromosorb W at 150° was employed in conjunction with a Varian Aerograph Model 90-P. All samples were trapped at −80° and immediately subjected to nmr analysis.

these cases of substituted imines.[9,10] Even though rapid isomerization is operative, the assignment of product distribution by pmr chemical shifts is attainable since the minor isomer must subject the N–CH_3 protons to the strongly shielding effect of the aromatic ring,[11] whereas the chemical shift of the N–CH_3 for the major *E* isomer will closely resemble the unsubstituted case **1e**.

Previously, it has been established *via* ^{13}C carbonyl chemical shifts of substituted acetophenones that ortho substituents induce twisting of the acetyl group from the plane of the aromatic ring by steric inhibition of resonance.[12] Since this deviation from coplanarity exists in the parent ortho-substituted ketones, the corresponding *N,N*-dimethylhydrazones (**1a–d**) should also deviate from planarity by a comparable degree, thus minimizing the proximate steric crowding caused by the ortho substituent. Removal of partial resonance stabilization associated with the aryl group allows the ketone derivatives to exist in both *E* and *Z* configurations, as in *N,N*-dimethylhydrazones of simple dialkyl ketones.[6b] Such steric interactions are not indicated for the 16 meta- and para-substituted acetophenone *N,N*-dimethylhydrazones which exist in the more stable *E* configuration, and in these cases neither heat nor treatment with acid gave evidence for the presence of the *Z* configuration.

The quaternization of **1a** with methyl iodide by standard procedures gave rise to an oil, which upon crystallization from ethanol–ethyl acetate yielded the (*E*)-2′-methoxyacetophenone *N,N,N*-trimethylhydrazonium iodide. The mother liquor was subsequently concentrated and the residue was recrystallized several times from enthanol at −70° giving the corresponding (*Z*)-methiodide. The nmr spectra are again useful in verifying both the structure and purity; the *Z* and *E* $-N^+(CH_3)_3$ moieties are evidenced by singlets at 3.29 and 3.61 ppm, which can easily be assigned to the *Z* and *E* isomers, respectively. The abnormally high field resonance is assigned to the nearly orthogonal group *Z* to the aromatic ring, while the more downfield absorption is assigned to the (*E*)-trimethylamine moiety. Neither of these methiodides isomerize upon heating at moderate temperatures but do hydrolyze slowly in aqueous media; thus the covalent bonding of the dimethylamino unshared electrons prevented their assistance in the geometrical isomerization.

The rapid geometric isomerization of these hydrazones adequately explains the fact that the *o*-haloacetophenone *N,N*-dimethylhydrazones give quantitatively 1,3-dimethyl-1*H*-indazole[2,13] after standing for several days at room temperature or heating in a sealed tube at 120° for several hours. The irreversible internal nucleophilic displacement possible only through the *Z* orientation would easily deplete the *E* isomer in this equilibrium mixture by converting it to the cyclized product, followed then by the elimination of methyl halide.[14]

Experimental Section[15]

The ortho-substituted acetophenone *N,N*-dimethylhydrazones were prepared according to the procedure described previously.[2] All spectral properties and microanalyses of the compounds were consistent with the assigned structures.[2]

(*Z*)- and (*E*)-2′-Methoxyacetophenone *N,N,N*-Trimethylhydrazonium Iodide.—A solution of 2′-methoxyacetophenone *N,N*-dimethylhydrazone [10 g, 52 mmol, bp 65–66° (0.1 mm)] and methyl iodide (20 g) in absolute ethanol (100 ml) was stirred under nitrogen for 2 days. The solvent was removed *in vacuo* affording a pale yellow semisolid which when washed with anhydrous ether gave the crude crystalline methiodide (14.2 g, 42.5 mmol) in 82% yield, mp 120–146°.

The crude methiodide was recrystallized twice from ethanol–ethyl acetate (2:1) yielding predominately the *E* isomer (4.2 g) as white needles: mp 158–159° dec; ir (KBr) 1628, 723 cm^{-1} (C=N); nmr (D_2O) δ 2.72 (s, CCH_3, 3 H), 3.61 (s, $N^+(CH_3)_3$, 9 H), 3.89 (s, $C_{arom}OCH_3$, 3 H), *ca.* 7.2 ppm (C_{arom}H, complex, 4 H).

Anal. Calcd for $C_{12}H_{19}N_2OI$: C, 43.12; H, 5.73; N, 8.38. Found: C, 43.06; H, 5.71; N, 8.18.

The mother liquor was concentrated *in vacuo* and recrystallized four times from absolute ethanol at −70° giving analytically pure the *Z* isomer: mp 140–141° dec; ir (KBr) 1640, 750 cm^{-1} (C=N); nmr (D_2O) δ 2.32 (s, CCH_3, 3 H), 3.29 (s, $N^+(CH_3)_3$, 9 H), 3.89 (s, $C_{arom}OCH_3$, 3 H), *ca.* 7.3 (C_{arom}H, 4 H).

Anal. Calcd for $C_{12}H_{19}N_2OI$: C, 43.12; H, 5.73; N, 8.38. Found: C, 43.10; H, 5.68; N, 8.43.

Registry No.—(*E*)-**1a**, 28541-35-7; (*Z*)-**1a**, 28541-36-8; (*E*)-**1b**, 28541-37-9; (*Z*)-**1b**, 28541-38-0; (*E*)-**1c**, 28541-39-1; (*Z*)-**1c**, 28541-40-4; (*E*)-**1d**, 28541-41-5; (*Z*)-**1d**, 28541-42-6; (*E*)-**1e**, 28541-43-7; (*Z*)-**1e**, 28541-44-8; (*Z*)-2′-methoxyacetophenone *N,N,N*-trimethylhydrazonium iodide, 28541-45-9; (*E*)-2′-methoxyacetophenone *N,N,N*-trimethoxyhydrazonium iodide, 28541-46-0.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(9) A. Mannschreck and U. Koelle [*Tetrahedron Lett.*, 963 (1967)] have recently suggested that the dipolar resonance structure a contributes to the ground state of dimethylhydrazones.

$$>C{=}NN(CH_3)_2 \longleftrightarrow >\bar{C}N{=}\overset{+}{N}(CH_3)_2$$
a

(10) The lateral-shift (inversion) mechanism *vs.* the rotational mechanism has been recently reviewed by Kessler [*Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970)].

(11) L. M. Jackman and S. Sternhall, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, pp 94–98.

(12) K. S. Dhami and J. B. Stothers, *Tetrahedron Lett.*, 631 (1964); *Can. J. Chem.*, **43**, 479 (1965).

(13) (a) E. Fischer and J. Tafel, *Justus Liebigs Ann. Chem.*, **227**, 303 (1885); (b) K. V. Auwers and M. Duesberg, *Ber.*, **53**, 1179 (1920).

(14) Other examples of similar geometrical isomerizations are known. See W. Borsche and W. Schriba, *Justus Liegibs Ann. Chem.*, **541**, 283 (1939), and W. Borsche and A. Herbert, *ibid.*, **546**, 293 (1941).

(15) Melting points were determined in sealed capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were measured in carbon tetrachloride solution with tetramethylsilane as the internal standard on a Varian A-60 instrument. Microanalyses were performed by Spang Microanalytic Laboratory, Ann Arbor, Mich.

Naphthyridine Chemistry. XIII. The Meisenheimer Reaction of the 1,5- and 1,6-Naphthyridine 1-Oxides

WILLIAM W. PAUDLER* AND DAVID J. POKORNY

Clippinger Laboratories, Department of Chemistry, Ohio University, Athens, Ohio 45701

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The Meisenheimer reaction of the 1,5-naphthyridine mono- and di-*N*-oxides has been reported[1,2] to afford

(1) E. V. Brown and A. C. Plasz, *J. Org. Chem.*, **32**, 241 (1967).

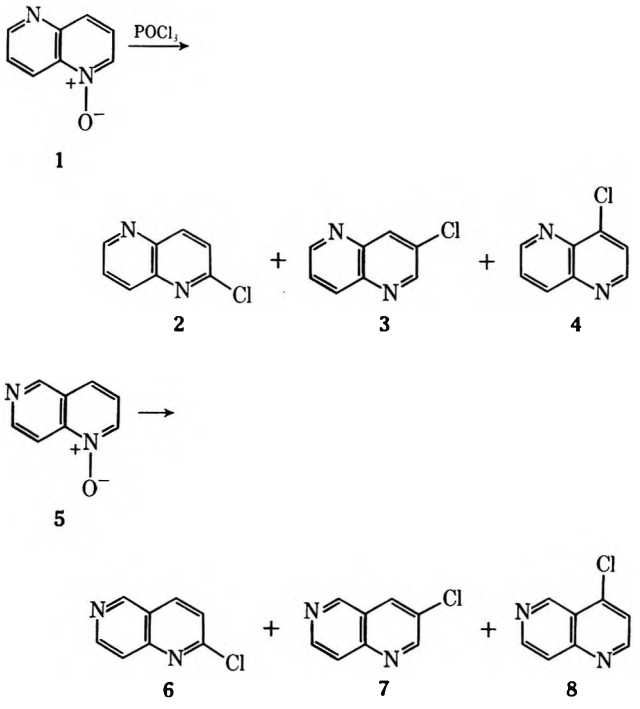
(2) E. P. Hart, *J. Chem. Soc.*, 1879 (1954).

the 2- (2) and 4-chloro-1,5-naphthyridine (4) from the mono-*N*-oxides 1 and the 2,6-dichloro-1,5-naphthyridine from the di-*N*-oxide.

Kobayashi, Kumadaki, and Sato[3] have described the formation of 5-chloro-1,6-naphthyridine as the lone product from the reaction of phosphoryl chloride with 1,6-naphthyridine 6-oxide, while, without isolation because of the reported lability, the 2-chloro-1,6-naphthyridine (6) has been described as the sole chloro isomer obtained when 1,6-naphthyridine 1-oxide (5) was subjected to the Meisenheimer reaction. When the Meisenheimer reaction was tried with 1,6-naphthyridine 1,6-dioxide, the 2,8-dichloro- and the 2,5-dichloro-1,6-naphthyridines were the only observed products.

In view of the fact that 5-nitroquinoline 1-oxide affords the 2-, 3-, and 4-chloro-5-nitroquinolines in the relative proportions 35:20:10 and the 6-nitroquinoline 1-oxide yields the three isomers in the ratio 16:35:56 when these *N*-oxides are treated with phosphoryl chloride,[4] it became of some interest to reexamine the Meisenheimer reaction of the 1-oxides of 1,5- and 1,6-naphthyridine.[5] We now wish to report the results of this study (*cf.* Scheme I).

SCHEME I



1,5-Naphthyridine 1-Oxide.—Reaction of 1,5-naphthyridine 1-oxide (1) with phosphoryl chloride results in a four-component mixture of bases, as shown by thin layer chromatography and gas chromatography. Quantitative gas chromatographic separation of this reaction mixture affords the two components with the longest retention time in their pure states. These compounds in the order of increasing retention time were identified respectively as 2-chloro- (2) and 4-chloro-1,5-naphthyridine (4). The other two components are present in the reaction mixture at too low a percentage to permit their direct isolation by preparative gas chromatography. Nevertheless, they were identified as 1,5-naphthyridine and 3-chloro-1,5-naphthyridine (3) by a comparison of their retention time, by behavior on tlc, and, in the case of the 3-chloro-1,5-naphthyridine (3), by the following procedure.

When the basic four-component mixture is treated with base, the 2- and the 4-chloro-1,5-naphthyridines (2 and 4, respectively) are hydrolyzed. To assure complete hydrolysis of the remaining small amount of the 4-chloro isomer 4, the chloroform extract of the aqueous base hydrolysis mixture [shown to contain 1,5-naphthyridine, traces of 4-chloro-1,5-naphthyridine (4), and the 3-chloro-1,5-naphthyridine (3)] was treated with sodium methoxide in methanol. The resulting mixture of 1,5-naphthyridine, 4-methoxy-1,5-naphthyridine, and 3-chloro-1,5-naphthyridine (3) was passed through an alumina column to afford pure 3-chloro-1,5-naphthyridine (3).

The latter compound was also prepared by the Eisch chlorination of 1,5-naphthyridine in a manner analogous to that described by us[6] for the bromination of 1,5-naphthyridine,

The 2-chloro- (2) and 4-chloro-1,5-naphthyridine (4) have been previously described,[2,7] and our compounds were shown to have properties identical with these chloro isomers.

The relative proportions of the four different components obtained by treatment of 1,5-naphthyridine 1-oxide with phosphoryl chloride were determined by gas chromatography.

Table I lists the average values of the relative proportions of these four compounds as obtained from five different experiments. The percentage composition is reproducible within 5% of the values given for each component.

Thus we find that the ratio of 4- to 2-chloro-1,5-naphthyridine obtained by us is 56:44 and is essentially identical with that reported by Brown (57:43).[1] The previously undetected 3-chloro isomer 3 is present to the extent of 3% of the total reaction products. The small amount (0.5%) of the parent compound is presumably formed by thermal deoxygenation of the *N*-oxide, since great care was taken to assure the absence of any 1,5-naphthyridine from the *N*-oxide reactant.

An interesting observation regarding the formation of the parent and the 3-chloro-1,5-naphthyridine (3) is the following: When the phosphoryl chloride is added *to* the 1,5-naphthyridine (1) without any cooling, the amounts of 3-chloro- (3) and parent 1,5-naphthyridines are about 7.5 and 3.5%, respectively. On the other hand, when the *N*-oxide is added slowly, and with cooling, to the phosphoryl chloride, the amount of 3-chloro- (3) product and parent 1,5-naphthyridine is decreased to 3.0 and 0.5%, respectively. The relative proportion of the 4-chloro- (4) and 2-chloro-1,5-naphthyridine (2) are, however, *unaffected* by this change

(3) Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.*, **17**, 1045 (1969).

(4) (a) G. B. Bachmann and D. E. Cooper, *J. Org. Chem.*, **9**, 302 (1944); (b) R. W. Gouley, G. W. Moersch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **69**, 303 (1947). (c) The formation of 3-chloro-6-nitroquinoline in this reaction has been questioned; *cf.* E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York N. Y., 1960, p 260.

(5) W. W. Paudler and T. J. Kress [*Advan. Heterocycl. Chem.*, **11**, 124 (1970)] have questioned the earlier results of the 1,5-naphthyridine 1-oxide products in the Meisenheimer reaction.

(6) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **33**, 1384 (1968).

(7) J. T. Adams, C. K. Bradsher, D. S. Breshlow, S. T. Amore, and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 1317 (1946).

TABLE I

RELATIVE PROPORTIONS OF THE MEISENHEIMER REACTION PRODUCTS OF THE 1-OXIDES OF 1,5- AND 1,6-NAPHTHYRIDINES

	Substituent					
Reactant	Nil	2-Chloro	3-Chloro	4-Chloro	2-Methoxy	4-Methoxy
1,5-Naphthyridine 1-oxide	0.5	42.3	3.0	54.2[a]		
1,6-Naphthyridine 1-oxide	2.0	12.0	20.0	66.0[a]		
1,6-Naphthyridine 1-oxide	4.0		21.0		11	64[b]

[a] These values were obtained by means of gc analysis. [b] These values were obtained from an analysis of the nmr spectrum of the reaction mixture and are, of course, less accurate than the gc data.

in the mode of addition. The data reported in Table I represent the values obtained by the latter mode of addition.

The temptation thus may be great to suggest that the 3-chloro-1,5-naphthyridine (**3**) is formed by electrophilic chlorination of 1,5-naphthyridine. However, when 1,5-naphthyridine itself is treated with phosphoryl chloride, even under more severe conditions than were employed in the Meisenheimer reaction, *no* reaction takes place and the 1,5-naphthyridine is recovered quantitatively. Whether the 3-chloro group actually enters the nonoxidized ring (structure 1, position 7) or the oxidized one (position 3) is, at present, a moot point. However, since the nitroquinoline 1-oxides also afford the 3-chloro isomer, one might suggest that it is, in fact, the 3 position of the 1,5-naphthyridine 1-oxide (**1**) that is involved.[4c]

1,6-Naphthyridine 1-Oxide.—The reaction of 1,6-naphthyridine 1-oxide (**5**) with phosphoryl chloride also affords four basic components, as established by gas chromatography. These components, in order of increasing retention times, are 1,6-naphthyridine, 3-chloro- (**7**), 4-chloro- (**8**), and 2-chloro-1,6-naphthyridine (**6**), respectively. The identity of these compounds was established by comparison with authentic samples.[3,8] Thus, contrary to the literature report[4] which claims the sole formation of the 2-chloro isomer, we find that in fact the 4-chloro and the 3-chloro isomers are formed as the major products in this reaction.

Since the possibility exists that the work-up might have caused the hydrolysis of substantial amounts of the 2- and 4-chloro-1,6-naphthyridines (**6** and **8**), we assured ourselves of the fact that this is not the case by modifying the work-up of the reaction mixture in such a manner so that no water was present. When this was done by adding methanol to the reaction mixture and the resulting solution was heated in the presence of sodium methoxide, there was isolated 2- and 4-methoxy-1,6-naphthyridine, along with the 3-chloro-1,6-naphthyridine (**7**), in essentially the same relative proportions observed for the corresponding chloro isomers (*cf.* Table I). It is of some interest to compare these results with those obtained from the Meisenheimer reaction of the 5- and the 6-nitroquinoline 1-oxides.

While the relative abundance of the three chloro isomers from the 5-nitroquinoline 1-oxide reaction is 2 > 3 > 4, we find that the related 1,5-naphthyridine 1-oxide generates the three isomers in the sequence 4 > 2 > 3. This can be readily explained by the substantial steric effect caused by the 5-nitro group toward nucleophilic chlorination at the 4 position of the quinoline nucleus. However, it is not yet clear why the amount of 3-chloro-1,5-naphthyridine (3%) is so much less than the 3-chloro-5-nitroquinoline 1-oxide (20%).

The lack of analogy between the results obtained from the 6-nitroquinoline 1-oxide (4 > 2 > 3) and the 1,6-naphthyridine 1-oxide (4 > 3 > 2) is also not at all obvious and this too must await the results of other experiments on related quinoline and naphthyridine *N*-oxides.

Experimental Section[9]

1,5-Naphthyridine 1-Oxide (**1**).—To 1,5-naphthyridine (5.2 g, 40 mol) dissolved in 15 ml of 30% H_2O_2 was added 0.4 g of $Na_2WO_4 \cdot 2H_2O$ and the resulting solution was heated at 55° for 110 min. The reaction mixture was then cooled to 10° and 100 mg of activated MnO_2 was added in two portions within 30 min. The mixture was then stirred for an additional 30 min, after which time the solution no longer gave a positive test with starch–iodide paper. The solution was then made basic with Na_2CO_3 and extracted continuously with $CHCl_3$ for 12 hr. The dried (anhydrous $MgSO_4$) $CHCl_3$ extract was evaporated to dryness and the remaining pale-yellow residue was triturated with hot pentane (two 300-ml portions), followed by hot cyclohexane (two 500-ml portions). The remaining solid is essentially pure (tlc) 1,5-naphthyridine 1,5-dioxide (0.6 g, 10% of theory). The cyclohexane was twice clarified with activated charcoal and the filtrate was concentrated to 150 ml. Upon cooling, 2.3 g of 1,5-naphthyridine 1-oxide was collected. The filtrate afforded an additional 0.6 g of the mono-*N*-oxide upon further reduction of its volume to 40 ml [total yield 2.9 g, 67% of theory, mp 125–127° (lit.[1] 125–127°, prepared by preacetic acid oxidation of 1,5-naphthyridine)].

Meisenheimer Reaction of 1,5-Naphthyridine 1-Oxide (**1**).—The 1,5-naphthyridine 1-oxide (100 mg, 0.77 mol) was added to well-stirred, ice-cold, freshly distilled $POCl_3$ (8 ml). After being stirred for 5 min this mixture was heated in an oil bath (preheated to 120°) for 20 min. The excess $POCl_3$ was then removed under an aspirator vacuum. Traces of remaining $POCl_3$ were then removed by heating the reaction residue to 65° under an aspirator vacuum. To the remaining dark mass was then added a mixture of aqueous Na_2CO_3 and ice (10 ml and 10 g, respectively). After trituration of the material, the essentially clear, dark-brown solution was extracted with ice-cold $CHCl_3$ (five 50-ml portions). The twice dried (anhydrous $MgSO_4$) $CHCl_3$ extracts were then evaporated to dryness below 40° to afford a white crystalline residue (100 mg) of reaction products.

Tlc [alumina plates, ether–hexane (1:1)] of the reaction product showed four distinct spots (made visible by I_2 vapor). These spots in increasing order of their R_f values were identified as 1,5-naphthyridine and 4-chloro- (**4**), 2-chloro- (**2**), and 3-chloro-1,5-naphthyridine (**3**), respectively, by comparison with authentic samples. Gas chromatography (20 ft × $^3/_8$ in. aluminum column, packed with 20% SE-30 on Chromosorb W, column temperature 220°, flow rate 150 ml/sec) also afforded four peaks identified as 1,5-naphthyridine (retention time 10 min), 3-chloronaphthyridine (15.1 min), 2-chloronaphthyridine (16.1 min), and 4-chloro-1,5-naphthyridine (18.1 min).

(8) W. W. Paudler and T. J. Kress, *J. Heterocycl. Chem.*, **2**, 393 (1965).

(9) The gas chromatograph used in these studies was an Aerograph Model A-90P-3 connected to a Sargent SRG recorder equipped with a Disc Integrator. The pmr spectra were obtained with a Varian HA-100 instrument and are dilute solutions in $CDCl_3$. The melting points were obtained with a Thomas-Hoover melting point apparatus and are corrected. The elemental analyses of the 3-chloronaphthyridines were done by Mrs. V. Gindlesberger of this department.

Preparative gc on the same column afforded the 4- and 2-chloro-1,5-naphthyridines as pure compounds, mp 102–103° (lit.[1] 102–103°), mp 114–116° (lit.[1] 114–116°), respectively.

The 3-chloro-1,5-naphthyridine was obtained pure by the following procedure. A suspension of 1.9 g of the reaction mixture from this reaction in 40 ml of 12% NaOH was heated under reflux for 3 hr, and the resulting solution was continuously extracted with $CHCl_3$. The dried (anhydrous $MgSO_4$) extracts were evaporated to dryness to yield 0.19 g of a white crystalline residue. This material was shown (tlc, gc) to contain 3-chloro-, 4-chloro-, and parent 1,5-naphthyridine. The 4-chloro-1,5-naphthyridine was removed by heating the reaction mixture in methanolic CH_3ONa (50 ml, 1.00 g of CH_3ONa) for 4 hr. After removal of the solvent, the residue was dissolved in 20 ml of water and the solution was continuously extracted with $CHCl_3$. The contents of the $CHCl_3$ extracts were then placed on an alumina column (neutral grade III, 30 g) and the 3-chloro-1,5-naphthyridine (**3**) was eluted with 12% ether–hexane. In this manner, 53 mg of compound **3** (mp 90.5–91°) was obtained. This compound is identical with the 3-chloro-1,5-naphthyridine obtained by the Eisch procedure (*vide infra*). The per cent yields of compounds **4**, **3**, **2**, and 1,5-naphthyridine are 42.8, 2.6, 33.8, and 0.04%, respectively. The relative percentages of the four compounds obtained are listed in Table I. Essentially the same amounts of all of these compounds are also obtained when Brown's procedure, utilizing PCl_5–$POCl_3$, is employed.

Meisenheimer Reaction of 1,6-Naphthyridine 1-Oxide (5).—The 1-oxide **5** was prepared by the method described in ref 3 except that the excess H_2O_2 was decomposed as described in our preparation of 1,5-naphthyridine 1-oxide. When 1,6-naphthyridine 1-oxide (100 mg, 0.77 mm) was treated with $POCl_3$ for 2 hr and the reaction mixture was worked up as described for the 1,5-naphthyridine 1-oxide reaction, 96 mg of reaction products was obtained.

Tlc and gc (same conditions as described above) showed the presence of 1,6-naphthyridine, 3-chloro- (**7**), 4-chloro- (**8**), and 2-chloro-1,6-naphthyridine (**6**) in the relative percentages listed in Table I. The retention times on gc and the melting points of the compounds in the order mentioned are 11.9 min, 16.7 min (103–103.5°), 17.6 min [90° (lit.[9] 90°)], and 19.4 min [88–89° (lit.[3] 88°)]. The per cent yields of the compounds, in the order parent, **7**, **8**, and **6**, are 1.9, 9.1, 15.2, and 50.2%, respectively.

Formation of 2- (9) and 4-Methoxy-1,6-naphthyridine (10).—In order to ascertain that hydrolysis of neither the 2- nor the 4-chloro-1,6-naphthyridine takes place during the work-up, the procedure was modified in one experiment by "decomposing" the reaction products with methanol in place of water. The resulting methanolic solution was then refluxed in the presence of 500 mg of CH_3ONa for 4 hr. Evaporation of the reaction mixture afforded a solid residue. This residue was dissolved in 20 ml of water and the resulting solution was continuously extracted with $CHCl_3$. The dried (anhydrous $MgSO_4$) extracts were evaporated to dryness to afford 80 mg of products. An nmr spectrum of a $CDCl_3$ solution of this mixture was a composite of 4-methoxy-, 2-methoxy-, and 3-chloro-1,6-naphthyridine, along with traces of the parent compound. This composite spectrum was analyzed by comparison with suitable authentic samples.[9] The relative proportions of the component thus obtained are listed in Table I.

3-Chloro-1,5- and -1,6-naphthyridine (3 and 7).—Into an efficiently stirred solution of 130 mg (1 mmol) of the appropriate naphthyridine in 30 ml of CCl_4 cooled to 5° was bubbled Cl_2 gas for 15 min. The resulting mixture containing a white precipitate was heated to reflux and 180 mg of pyridine dissolved in 5 ml of CCl_4 was added over a 15-min period. After heating for an additional 24 hr, the cooled reaction mixture was filtered and the collected solid was digested with 10% sodium hydroxide (25 ml) for 1 hr. The solution was then extracted with CH_2Cl_2 and the extract was combined with the $CHCl_3$ filtrate. The combined solutions were evaporated *in vacuo* affording a tan solid.

Gas chromatographic separation under the conditions described for the separation of the Meisenheimer reaction products afforded the following compounds.

3-Chloro-1,5-naphthyridine: 16 mg, 10% yield, mp 90.5–91°. *Anal.* Calcd for $C_8H_5N_2Cl$: C, 58.37; H, 3.06; N, 17.02. Found: C, 58.49; H, 3.20; N, 17.22.

3,7-Dichloro-1,5-naphthyridine: 8 mg, 4% yield, mp 150–52°. *Anal.* Calcd for $C_8H_4N_2Cl_2$: C, 48.03; H, 2.01; N, 14.01. Found: C, 47.89; H, 2.11; N, 14.20.

3-Chloro-1,6-naphthyridine: 24 mg, 15% yield, mp 103–103.6°. *Anal.* Calcd for $C_8H_5N_2Cl$: C, 58.37; H, 3.06; N, 17.02. Found: C, 58.26; H, 2.89; N, 16.93.

No attempt was made at this point to isolate two other chloro-1,6-naphthyridines, presumably the 8-chloro and the 3,8-dichloro derivatives. Detailed studies of the Eisch chlorination procedure on numerous naphthridines along with analyses of their pmr spectra will be the subject of a forthcoming publication.

Registry No.—**1**, 27305-48-2; **3**, 7689-63-6; **5**, 23616-39-9; **7**, 28795-77-9; 3,7-dichloro-1,5-naphthyridine, 28795-78-0.

Piperidinodechlorination of Chloronitronaphthalenes. A Further Comparison between Nitro-Group and Aza-Group Activation[1]

GABRIELLO ILLUMINATI,* GIANCARLO SLEITER,* AND MAURIZIO SPERANZA

Department of Chemistry, The University of Rome, 00185 Rome, Italy, and Centro C.N.R. dei Meccanismi di Reazione, Rome, Italy

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The importance of specific solvation (H bonding) in the nucleophilic reactions of N-heteroaromatic substrates has been stressed in recent studies[2–5] and was suggested[3,5] to be a major differential feature between aza- and nitro-group activation, on the basis of the solvent effects observed in the reaction of 2- and 4-chloroquinoline with piperidine. The most appropriate comparison with the latter reaction requires the investigation of the nitronaphthalene analogs, which is the object of the present note.

The kinetics of the piperidinodechlorination of 2- and 4-chloro-1-nitronaphthalene have been studied in toluene, ethyl acetate, piperidine, methanol, and dimethyl sulfoxide. The reactions in ethyl acetate were followed as long as the piperidinolysis of the solvent[3,6] remained kinetically unimportant. Possible solvolysis in methanol solution[7] could be excluded either by product analysis or by an indirect method.[8] The reactions of the compounds investigated yielded the expected products and followed regular second-order or pseudo-first-order kinetics, in agreement with previous studies.[9] With the reaction of 4-chloro-1-nitronaphthalene in toluene, initially linear kinetic plots eventually became erratic after some 50–60% reaction, probably because thermal decomposition of the substrate occurred.[10] The second-order rate constants at varying temperatures and the activation parameters for 2- and 4-chloro-1-nitronaphthalene are collected in Table I.

(1) Nucleophilic Heteroaromatic Substitution. XXXV.
(2) G. Illuminati and G. Marino, *Chem. Ind. (London)*, 1287 (1963).
(3) G. Illuminati, G. Marino, and G. Sleiter, *J. Amer. Chem. Soc.*, **89**, 3501 (1967).
(4) F. Genel, G. Illuminati, and G. Marino, *ibid.*, **89**, 3516 (1967).
(5) G. B. Bressan, I. Giardi, G. Illuminati, P. Linda, and G. Sleiter, *J. Chem. Soc. B*, 225 (1971).
(6) E. M. Arnett, J. G. Miller, and A. R. Day, *J. Amer. Chem. Soc.*, **72**, 5635 (1950).
(7) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951); H. Suhr, *Tetrahedron Lett.*, 5371 (1966).
(8) E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.*, 3392 (1953).
(9) M. Simonetta and P. Beltrame, *Gazz. Chim Ital.*, **88**, 769 (1958).
(10) E. Berliner, M. J. Quinn, and P. J. Edgerton, *J. Amer. Chem. Soc.*, **72**, 5305 (1950).

TABLE I

SOLVENT EFFECTS ON THE PIPERIDINODECHLORINATION REACTION AT 90°

Substrate	Solvent	10^5k[a]	E_{act}[b]	$-\Delta S^{\ddagger}$[c]
2-Chloro-1-nitronaphthalene[d]	Toluene	25.7	13.9	39
	Ethyl acetate	38.0	12.0	44
	Methanol	16.0	18.1	29
	Piperidine	46.6[e]	11.8	43
	Dimethyl sulfoxide	345[e]	10.8	42
4-Chloro-1-nitronaphthalene[f]	Toluene	0.265[e]	13.7	49
	Ethyl acetate	5.55[e]	9.95	53
	Methanol	27.4	14.4	38
	Piperidine	7.73[e]	9.08	54
	Dimethyl sulfoxide	1550[e]	10.0	41

[a] k = rate constants in l. mol^{-1} sec^{-1}. [b] In kcal/mol. [c] In eu. [d] Additional 10^5 k values (temp, °C): in toluene, 4.48 (60.0), 8.34 (70.0), 14.5 (80.0); in ethyl acetate, 22.4 (80.0), 55.5 (100.0), 87.5 (110.0); in methanol, 3.74 (70.0), 7.73 (80.0), 30.7 (100.0); in piperidine, 0.211 (0.0), 0.461 (10.0), 0.744 (17.0), 1.27 (25.0), 3.44 (40.0); in DMSO, 9.62 (20.0), 18.0 (30.0), 32.5 (40.0), 53.0 (50.0). [e] Calculated from Arrhenius parameters. [f] Additional 10^5 k values (temp, °C): in toluene, 2.57 (140.0), 3.37 (150.0), 5.42 (160.0), 11.0 (180.0); in ethyl acetate, 15.9 (120.0), 21.8 (130.0), 29.6 (140.0), 38.7 (150.0); in methanol, 15.5 (80.0), 47.7 (100.0), 76.2 (110.0); in piperidine, 0.382 (20.0), 0.661 (30.0), 1.06 (40.0), 1.63 (50.0); in DMSO, 56.0 (20.0), 103 (30.0), 163 (40.0), 280 (50.0).

TABLE II

DIFFERENTIAL SOLVENT EFFECTS IN THE NITRONAPHTHALENE AND AZANAPHTHALENE SYSTEMS

	Toluene (T)	Ethyl acetate (EA) k_{EA}/k_T	Piperidine (P) k_P/k_T	Methanol (M) k_M/k_T	Dimethyl sulfoxide (DMSO) k_{DMSO}/k_T
	Solvent Effects Relative to Toluene				
2-Chloro-1-nitronaphthalene (I)[a]	1	1.48	1.81	0.62	13.0
2-Chloroquinoline (II)[b]	1	2.47	7.68	6.02	54.8
4-Chloro-1-nitronaphthalene (III)[a]	1	21.8	29.1	103	5850
4-Chloroquinoline (IV)[b]	1	11.3	16.9	458	1700
	Relative Activating Power				
I *vs.* II, k_{NO_2}/k_{aza}[c]	63	38	15	6.5	15
III *vs.* IV, k_{NO_2}/k_{aza}[c]	51	94	88	11	176

[a] At 90.0°. [b] Values at 86.5°, taken from ref 3. [c] Evaluated from the rate constants at 86.5°; values for the quinolines were taken from ref 3.

A comparison of 2- and 4-chloro-1-nitronaphthalene with 2- and 4-chloroquinoline, respectively, with regard to solvent effects on reactivity, is reported in Table II. As expected, with both types of substrates the reactivities in the diverse solvents are less broadly spaced in the 2-chloro than in the 4-chloro isomer, as a result of a "built-in" solvation effect.[11] This effect is particulary strong with 2-chloro-1-nitronaphthalene [in fact, it is stronger than with either 2-chloroquinoline (α-aza effect) or 2-chloro-1-nitrobenzene[12]] and is most evident when comparing solvents of markedly different polarity (see, for example, the k_{DMSO}/k_T values in Table II).

In the aprotic solvents, the reactivity is in the order DMSO > ethyl acetate > toluene, as expected[13] from the polarity of the medium. This order is analogous to the one observed with the quinoline compounds. Despite its basic character, piperidine is only a slightly "faster" solvent than ethyl acetate of the same polarity. This observation suggests that the basic properties of DMSO[14] are probably not a major factor in the rate-enhancing effect of this solvent, which is likely to solvate ionic transition states.[15] It should be noted that the reaction of the 4-chloro isomer in this solvent is accompanied by a relatively high entropy of activation.

In contrast, an important difference between the two types of substrates is observed in methanol. Whereas the reactivity in the aprotic solvents *relative* to toluene is greater for 4-chloro-1-nitronaphthalene than for 4-chloroquinoline (Table II), in methanol solution the reverse is true. This confirms the different importance of the hydroxylic solvent in the two types of substrates, as suggested in a previous comparison.[3] We attribute this difference to a greater rate-enhancing H-bonding solvent–substrate interaction in the case of the quinoline compound. In the nitro-activated compounds such an interaction is so much weaker as to become overshadowed in the 2-chloro isomer by other factors; in this case, the reaction rate in methanol is lower than in toluene solution (k_M/k_T = 0.62). An inverted order of this kind has been noted previously under similar conditions,[16] but is not found with 2-chloroquinoline, where the influence of the solvent may still include appreciable specific solvation with the heterocyclic nitrogen. A major opposing factor tending to lower the overall reactivity in methanol solution is the reduced effective nucleophilic power of piperidine due to H-bonding solvent–nucleophile interaction.[17] This effect may be responsible for the observed changes in the activation parameters, *i.e.*, higher energies and entro-

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pies of activation for the reactions in methanol solution relative to other solvents.

In the light of the reactivity pattern displayed in methanol solution, the similar behavior of piperidine to that of ethyl acetate, as noted above, indicates that the former solvent is not sufficiently protic to promote any appreciable specific solvent–substrate interaction.

Since the reaction rates are different functions of the solvent depending on both the activating group and its position relative to the reaction site, the activating power of the nitro group relative to that of the aza group also depends on the solvent, as shown by the k_{NO_2}/k_{aza} ratios reported in Table II, which display variations of more than one order of magnitude. In particular, the lowest values were obtained for the reactions in methanol solution, where a major contribution to this effect comes from the greater H-bonding interaction observed with the N-heteroaromatic substrates. It is of interest to note that, on comparing the reactivity of the nitrobenzene with that of the pyridine series in methanol, the k_{NO_2}/k_{aza} ratio is greater at the ortho than at the para positions,[18] but the reverse is true for the corresponding fused-ring systems considered here.

Experimental Section

Materials.—2-Chloro-1-nitronaphthalene, mp 95.5–96.5° (lit.[16] mp 99°), and its 4-chloro-1-nitro isomer, mp 84.5–85.5° (lit.[19] mp 87°), were prepared from the appropriate nitronaphthylamines by the methods of Hodgson and Walker[20] and of Bassilios and Shawky,[21] respectively. The products expected from the reactions under kinetic investigation were prepared by refluxing the chloronitronaphthalenes in neat piperidine for about 2 hr: 4-nitro-1-piperidinonaphthalene, mp 75–76° (lit.[22] mp 76°), and 1-nitro-2-piperidinonaphthalene, mp 63.5–64° (red needles from methanol).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.3; H, 6.3; N, 10.9. Found: C, 70.5; H, 6.4; N, 11.0.

Dimethyl sulfoxide (Erba-RP) was purified by allowing it to percolate slowly in the dark through a 1-m column filled with molecular sieve "Bayer T10" (Schuchardt), water content *ca.* 30 ppm. Methanol,[23] piperidine,[24] toluene,[25] and ethyl acetate[26] were purified as in the given references.

Product Analyses.—The mixtures from the kinetic measurements were analyzed by tlc. Single spots were found except in the high-temperature reactions of 4-chloro-1-nitronaphthalene in toluene solution after 57% reaction at 140°, 62% at 150°, 69% at 160°, and 84% at 180°. No further investigation on the by-products was made.

Kinetic Measurements.—The general procedure used has been described previously.[3,23,24] The reaction rates were followed by analyzing for the displaced chloride ion. Samples were quenched in 10 ml of 2 *N* nitric acid (3 *N* when piperidine was the solvent); sufficient acetone was added to dissolve any organic material; and the homogeneous solutions were titrated by the potentiometric method.[3,27] The rate constants were obtained graphically from second-order or pseudo-first-order plots. All the second-order rate constants were corrected for the thermal expansion of the solvent. Activation energies and entropies were calculated from the k values at four or five temperatures, using the least-squares method. Values of k are accurate to ±2.5% or better, energies of activation to ±0.4 kcal/mol, and values of $\Delta S^{\pm}$ to ±1 unit.

Registry No.—I, 4185-63-1; II, 612-62-4; III, 605-61-8; IV, 611-35-8; 1-nitro-2-piperidinonaphthalene, 7711-41-3.

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Reduction of Diazonium Fluoroborates in Dimethylformamide, Catalyzed by Rhodium Complexes

GERARD S. MARX

Department of Organic Chemistry, Hebrew University, Jerusalem, Israel

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I wish to report on a novel reduction of aromatic diazonium fluoroborates to arenes by DMF, a reaction which is catalyzed by $RhCl(CO)(PPh_3)_3$ (RCCP) and $RhCl(PPh_3)_3$ (RCTP) at room temperature and at 80°.

$$ArN_2^+BF^{-4} \xrightarrow{\text{Rh complex, DMF}} ArH$$

Electron-attracting substituents appear to favor this reduction, whereas, in the one observed case of a strong electron-donating substituent (OMe), no reduced product was observed. Ortho substitution (NO_2, CO_2Et, Me) did not appear to affect significantly the yield of reduced product. In fact, in the case of the 2-methyl-4-nitrobenzenediazonium salt, the reduction competed successfully with the spontaneous cyclization to 6-nitroindazole.[1]

Addition of small amounts of water or formic acid to the DMF lowered the yields of the reduction products. Reduction was not observed in the absence of the Rh complex.

Only traces of fluorinated compounds were detected in the products by elemental analysis, vpc, or tlc, whether the reactions were carried out at room temperature or at 80°[2] (see Table I).

A few other solvents were tested, *viz.*, dimethylacetamide (DMA), acetonitrile, and, in one case, formamide. Only in formamide was the same reduction process observed. This points to the formyl hydrogen of DMF or formamide as the source of the hydrogen involved in the reduction.[3] An ir study of RCCP has shown that a hydrido–rhodium complex may be an intermediate in this reaction; a solution of RCCP in DMF develops, in addition to the C=O peak at 1970 cm^{-1},[4] a peak at 2100 cm^{-1}, which is transformed within 24 hr into a broad envelope with a maximum at 2150 cm^{-1}. On the other hand, a similar solution of RCCP in DMA showed only the initial peak at 1970

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(2) In experiments with the diazonium fluoroborate derived from ethyl-3-amino-2-naphthoate in DMF with RCCP for 2 days at room temperature, the product (30% yield) after work-up was a mixture of 17% 2-naphthoic acid and 13% 3-fluoro-2-naphthoic acid. This result agrees with a previous report from this laboratory [J. Blum, *Israel J. Chem.*, **4**, 158 (1966)] in which also *p*-tolyl- and 1-naphthyldiazonium fluoroborates reacted with RCTP in DMF to give *p*-fluorotoluene and 1-fluoronaphthalene. We are unable, at this time, to rationalize this divergence in results.
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TABLE I

CATALYTIC REDUCTION OF DIAZONIUM FLUOROBORATE, $ArN_2 \cdot BF_4$ (TO ArH)

Ar	Registry no.	Solvent[a]	Catalyst	Temp,[d] °C	% yield of ArH[b]
2-$NO_2 \cdot C_6H_4$	365-33-3	DMF	RCCP		43
3-$NO_2 \cdot C_6H_4$	586-36-7	DMF	RCCP		34
4-$NO_2 \cdot C_6H_4$	456-27-9	DMF	RCCP		50
4-$NO_2 \cdot C_6H_4$		DMF	RCTP		23
4-$NO_2 \cdot C_6H_4$		DMA	RCCP		0
3-Cl·C_6H_4	14874-10-3	DMF	RCCP		75
3-Cl·C_6H_4		DMF	RCTP		50
3-Cl·C_6H_4		DMA	RCCP		0
4-Cl·C_6H_4	673-41-6	DMF	RCCP		47
2-$CO_2Et \cdot C_6H_4$	28912-87-0	DMF	RCCP		54
2-$CO_2Et \cdot C_6H_4$		CH_3CN	RCCP		0
4-$CO_2Me \cdot C_6H_4$	369-48-2	DMF	RCCP		44
4-$CH_3 \cdot C_6H_4$	459-44-9	DMF	RCCP		10[c] + trace ArF
4-$CH_3 \cdot C_6H_4$		DMF	RCTP		7[c] + trace ArF
4-MeO·C_6H_4	18424-07-2	DMF	RCCP		10
2-CH_3-, 4-$NO_2 \cdot C_6H_4$	15278-77-0	DMF	RCCP		61
2-CH_3-, 4-$NO_2 \cdot C_6H_4$		Formamide	RCCP		23
3-NO_2-, 4-Me·C_6H_4	28912-92-7	DMF	RCCP		42
$C_{10}H_7$	28912-93-8	DMF	RCCP		16
$C_{10}H_7$		DMF	RCCP	80	20
$C_{10}H_7$		CH_3CN	RCCP		0
$C_{10}H_7$		CH_3CN	RCCP	80	0
$C_{10}H_7$		DMF	RCTP		20
$C_{10}H_7$		DMF	RCTP	80	22
$C_{10}H_7$		CH_3CN	RCTP		0
$C_{10}H_7$		CH_3CN	RCTP	80	0

[a] All solvents were dried over CaH_2 and distilled. [b] Yields based on vpc or tlc and elemental analyses. [c] Only by vpc. [d] Room temperature unless otherwise specified.

cm^{-1} and no new peaks in the 2700–1800-cm^{-1} region. The hydrido-complex $RhH(CO)(PPh_3)_3$ in DMF has peaks at 2450 cm^{-1} (RhH) and 1970 cm^{-1} (C=O), with no new peaks appearing even after prolonged standing.

Experimental Section

A mixture of 2 mmol of ArN_2BF_4 and 0.12 mmol of RCCP or RCTP in 5 ml of dry solvent was left at room temperature for 2 days, or at 80° for 1 day. The reaction mixture was poured into water and extracted with benzene or ethyl acetate and the extract was washed with 3 *N* NaOH and water and dried over $MgSO_4$. The crude products were chromatographed on a short column of silica gel or alumina, after which they were checked by vpc or tlc and elemental analysis. The ir spectra were run on a Perkin-Elmer Model 137 NaCl spectrophotometer.

Registry No.—RCCP, 28912-94-9; RCTP, 14694-95-2.

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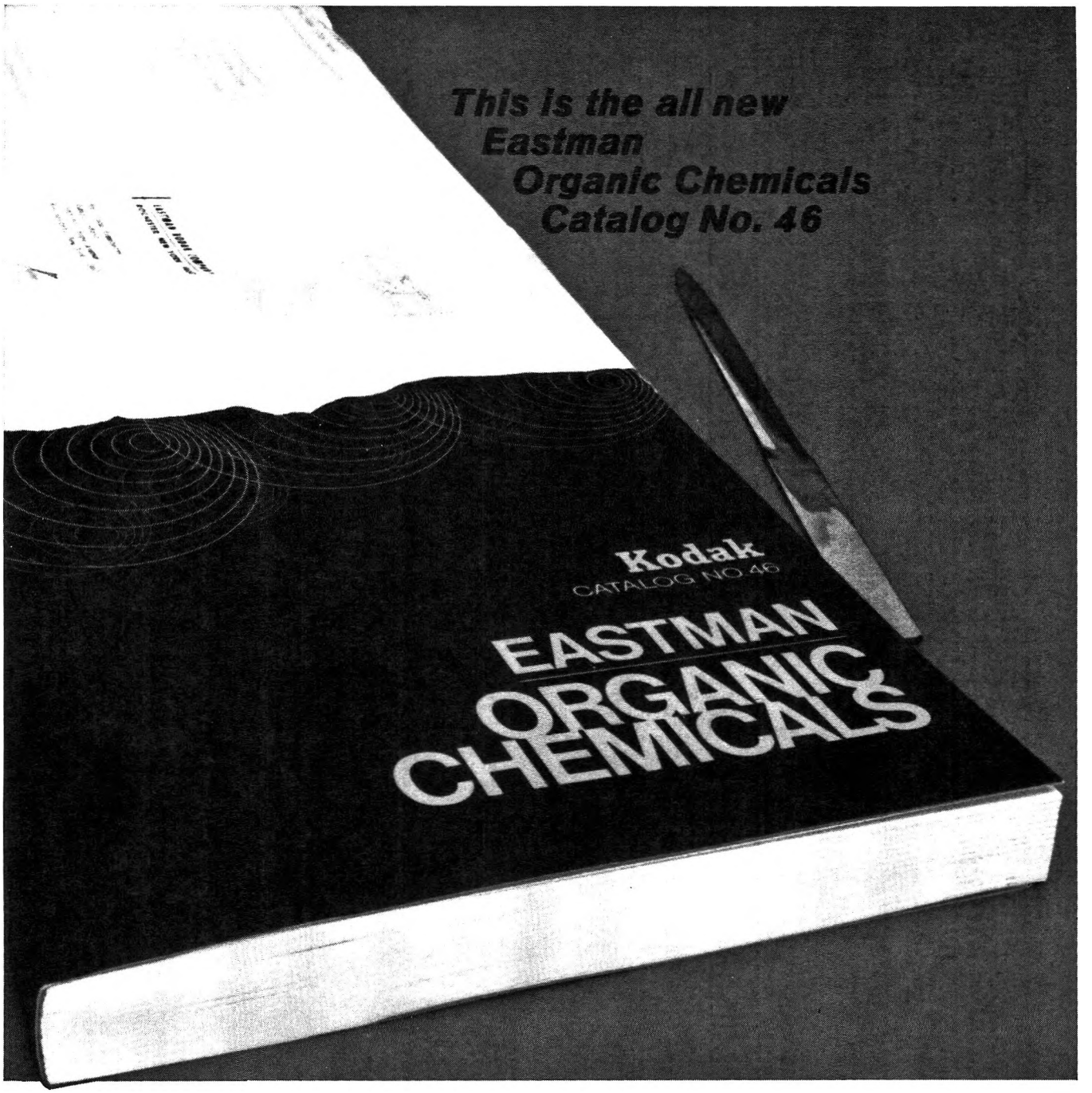

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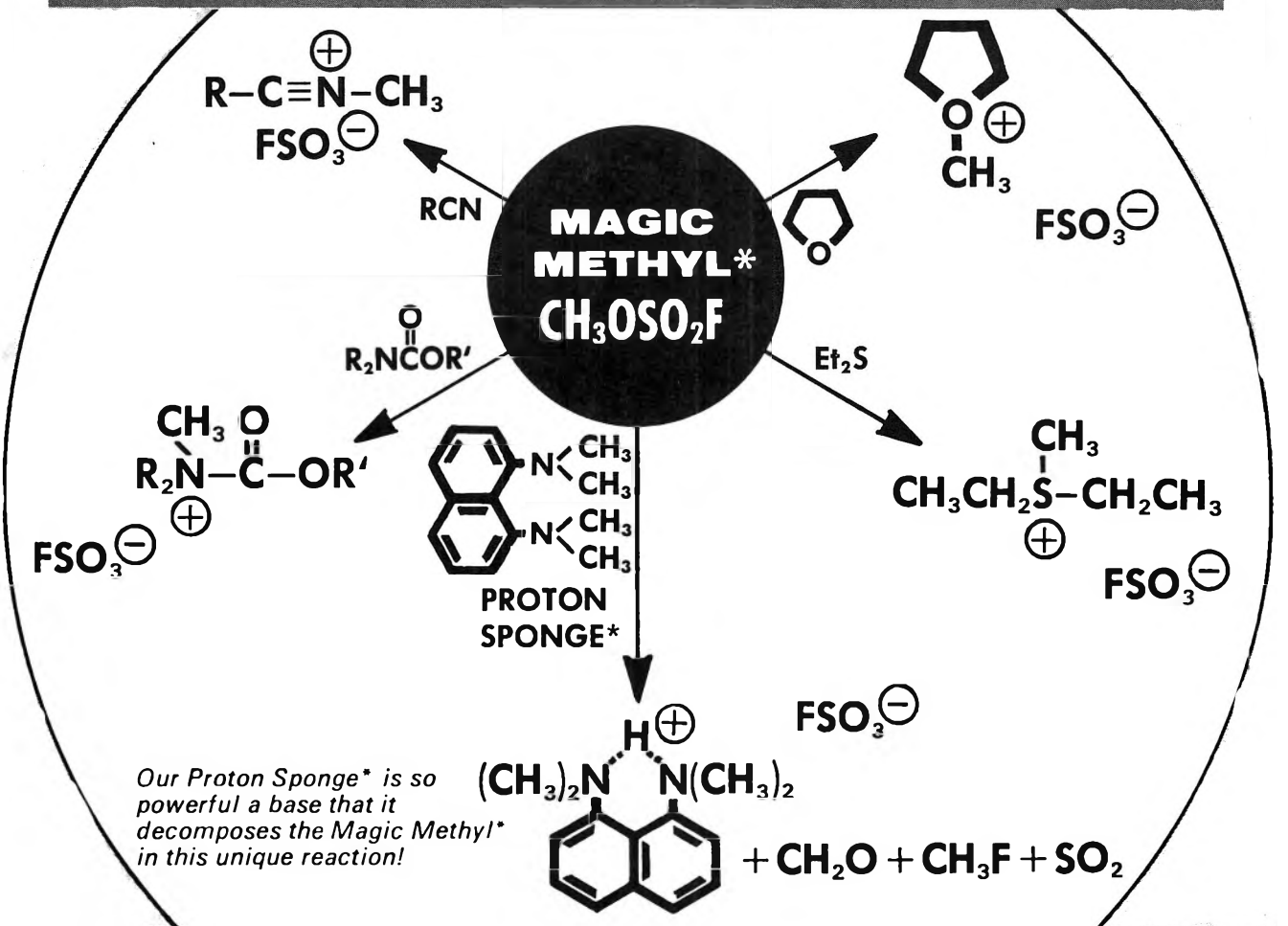

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