identifiable material obtained was 26 mg. of the acetate of the keto alcohol XVIIId, an oil: infrared (film), 5.72 (s), 5.85 (s) $\mu$ (C=O); p.m.r., 3-proton singlet at 1.96 p.p.m. ($CH_3COO$) and 2-proton $A_2$ part of $A_2B_2$ multiplet at 4.0 p.p.m. ($CH_2OAc$).

**C.**—To a solution containing 835 mg. of the keto alcohol XVIIId in 25 ml. of acetone was added 14 ml. of chromic acid[39] solution at 25°, to which, after standing for 30 min., water was added and the solution was extracted with ether. The ether extract was washed with three 25-ml. portions of 10% sodium carbonate solution which afforded 361 mg. of keto acid XVIIIb on appropriate work-up. The neutral faction consisted of 355 mg. of material showing two major spots on thin layer chromatography and as yet unidentified.

**Enol Lactone XXII. A.**—A solution of 300 mg. of the keto acid XVIIIb in 10 ml. of acetic acid–acetic anhydride (4:1) was cooled to 0° and 6 drops of boron trifluoride etherate was added. The solution was stirred for 1 hr. at 0° and 15 hr. at room temperature. The addition of water gave 240 mg. of a precipitate which was filtered off and washed well with water. Crystallization of the precipitate from hexane gave 210 mg. of the pure enol lactone XXII: m.p. 127–128°; infrared ($CCl_4$), 5.52 (s) (C=O) and 5.84 (s) $\mu$ (C=C); and p.m.r., 2-proton singlet at 2.05 p.p.m. ($-CH_2-OCO-$).

**B.**—A solution of 30 mg. of the keto acid XVIIIb in 5 ml. of acetyl chloride was refluxed for 48 hr. Removal of the acetyl chloride *in vacuo* left a white solid which crystallized from hexane to give 21 mg. of the enol lactone XXII, m.p. 124–126°, which was identical in all respects with that obtained by procedure A.

**Acknowledgment.**—The authors are indebted to the National Science Foundation for financial support of this work, to Dr. Dwight E. Leavens for a generous sample of pimaric acid, and to Messrs. J. Stevens and R. V. Stevens for technical assistance.

# An Approach to Ring E of Reserpinoid Substances

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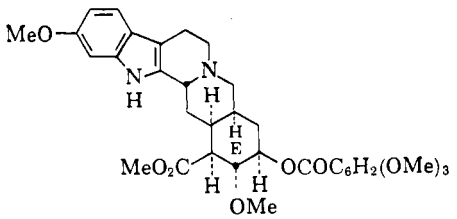
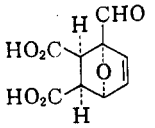
The preparation and reactions of a lactone acid containing many of the functional features of ring E of reserpine are described. The structure determination of this acid by the degradation of one of its derivatives to an aromatic compound and the latter's synthesis from hemimellitic acid are presented.

The elucidation of the stereochemistry of the medicinally important Rauwolfia alkaloid reserpine (I)[4] led us in 1955 to attempt its total synthesis.[5] A route fo synthesis leading first to the stereochemically crucial ring E of the alkaloid system was formulated and the aldehydo ester IV containing four of its five asymmetric centers in the required relative configuration was designated as the primary goal. The choice of IV was predicted on the assumption that the unnecessary ether linkage $\alpha$ to the aldehyde function would be cleaved by reduction and that only a few standard chemical processes would stand between the reduction product and the alkaloid. Furthermore, the ester IV appeared, at least in principle, to be derivable readily from furfural by Diels–Alder reaction with maleic acid or its derivatives, by halolactonization of the adduct II and reduction, and by Arndt–Eistert homologation of the resulting lactone III.

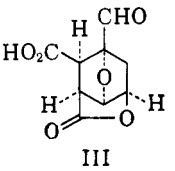
Past experience on the behavior of furans in the Diels–Alder reaction[6] placed severe limitations on the scope of the above scheme of synthesis. Whereas maleic anhydride was our preferred dienophile, we were restricted to the use of maleic acid, since on reaction with furan the anhydride has been reported to yield only *exo* product while the acid had afforded *endo* product,[7] a substance of the configuration needed for our compounds. Further, the recorded lack of reactivity of furfural in the Diels–Alder reaction[5] led us to the use of furfuryl alcohol and its relatives as dienes. While maleic acid interaction with furfuryl alcohol or its acetate resulted only in resinification of the furan derivatives, reaction of the acid with N-furfuryl acetamide, followed by exposure of the aqueous solution of the adduct to iodine and sodium bicarbonate,[8] led to a single iodo lactone in high yield.[9] It was hoped that its nitrogenous side chain would be amenable later to conversion to the desired carboxaldehyde unit (conceivably by deamination *via* an N-nitrosoamide intermediate and later oxidation).



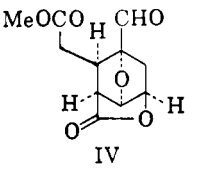

I




II




III




IV

(1) Postdoctoral Fellow, 1954–1956.

(2) To whom inquiries should be addressed: 56 Murdock St., Fords, N. J.

(3) Public Health Service Predoctorate Fellow, 1959–1960.

(4) C. F. Huebner and E. Wenkert, *J. Am. Chem. Soc.*, **77**, 4180 (1955); P. A. Diassi, F. L. Weisenborn, C. M. Dylion, and O. Wintersteiner, *ibid.*, **77**, 4687 (1955); E. E. van Tamelen and P. D. Hance, *ibid.*, **77**, 4692 (1955). For a full review *cf.* P. E. Aldrich, *et al.*, *ibid.*, **81**, 2481 (1959).

(5) *Cf.* R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *ibid.*, **78**, 2023, 2657 (1956); *Tetrahedron*, **2**, 1 (1958).

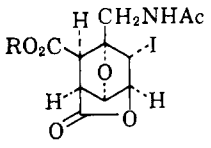
(6) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953.

(7) R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948), and references contained therein.

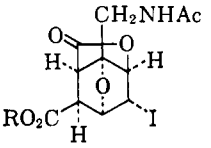
(8) *Cf.* C. D. Ver Nooy and C. S. Rondestvedt, Jr., *ibid.*, **77**, 3585 (1955).

(9) Maleic acid underwent no reaction with furfuryl amine or its N-benzoyl or N-benzenesulfonyl derivatives, although the failure of the amides to react may have been due mainly to their poor solubility in the aqueous reaction medium. On the other hand, a reaction between maleic acid and the N-carbobenzoxy derivative followed by iodolactonization yielded a mixture from which a crystalline iodo lactone (m.p. 106–108°; methyl ester, m.p. 103–104°) could be isolated. However, further study on this substance was abandoned in favor of an investigation of the product from N-furfurylacetamide.

If by analogy with the furan model[7] it be assumed that the Diels–Alder reaction had yielded an *endo* product, structure Va or VIa could be assigned to the iodo lactone, although no reason for the formation of only one of the two possible lactones could be cited, Since it was expected that the chemistry of the iodo lactone would reveal its structure, no separate structure analysis was started at this time. Instead, the product was hydrogenolyzed and the general chemical behavior of the resulting lactone VIIa was investigated.[10]

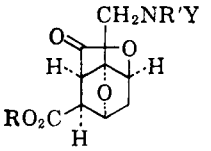


V



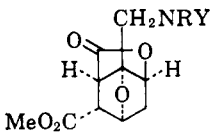
VI

a, R = H
b, R = Me



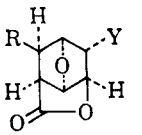
VIIa, R = R′ = H; Y = Ac
b, R = R′ = Y = H
c, R = R′ = H; Y = $SO_2C_6H_5$
d, R = Me; R′ = H; Y = Ac
e, R = Me; R′ = H; Y = $SO_2C_6H_5$
f, R = R′ = Me; Y = $SO_2C_6H_5$

Acid hydrolysis of VIIa yielded an amino acid VIIb, whose acetylation reverted it to VIIa. Benzenesulfonylation afforded VIIc. Diazomethane treatment of VIIa gave the ester VIId, while long exposure of VIIa to ethereal diazomethane produced the stereoisomer VIIa. Undoubtedly a trace of methylamine in the ether solution, carried along from the diazomethane preparation, was responsible for the isomerization, since a conversion of VIId into VIIIa was accomplished readily by triethylamine in acetonitrile solution. Diazomethane treatment of the sulfonamide VIIc for a short time afforded the ester VIIe and, for a somewhat longer time, the N-methyl derivative VIIf, while long exposure resulted in the formation of the isomer VIIIb.



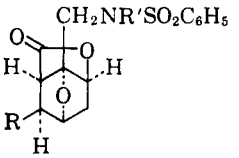
VIIIa, R = H; Y = Ac
b, R = Me; Y = $SO_2C_6H_5$

Arndt–Eistert homologation of the acid VIIa failed in its first step. Neither thionyl chloride treatment of VIIa nor oxalyl chloride treatment of its sodium salt yielded the desired acid chloride. Since the unrecognizable products of these reactions could have been a consequence of intramolecular interaction of the acid chloride or its precursors with either the lactone or acetamido moieties (the latter only in case VIIa were actually desiodo Va), the Arndt–Eistert homologation of a model compound was investigated. The product of iodonation (IXa) of the furan–maleic acid adduct was hydrogenolyzed. Esterification of the reduced compound IXb by diazomethane treatment or by successive treatments with thionyl chloride and with methanol yielded the ester IXc. Exposure of the acid chloride to diazomethane and of the resultant diazo ketone to silver oxide in methanol led to the ester IXd. This successful homologation pointed to the acetamido unit as the interfering group in the attempted Arndt–Eistert synthesis with VIIa and suggested a study of the homologation of VIIc.



IXa, R = $CO_2H$; Y = I
b, R = $CO_2H$; Y = H
c, R = $CO_2Me$; Y = H
d, R = $CH_2CO_2Me$; Y = H

Treatment of the acid VIIc with thionyl chloride and thereafter with methanol yielded the ester VIIe. This proof of the intermediacy of an acid chloride was exploited by exposure of the chloride to diazomethane and then to methanolic silver oxide, reaction sequence which led to a mixture of the homologous ester Xa and its N-methyl derivative Xb. Formation of the latter, also readily prepared by diazomethane treatment of Xa, could be suppressed greatly by rapid removal of the excess diazomethane used in the generation of the intermediate diazo ketone. Exposure of the diazo ketone to hydrogen chloride yielded the chloro ketone Xc. A variety of reactions designed to cause intramolecular interaction of the benzenesulfonamidomethyl side chain with the newly created side chains of Xa and Xc were attempted, but failed. While negative results, these represented the first serious indication that we were dealing with compounds based on the undesirable structure VIa (rather than Va) of the starting iodo lactone.

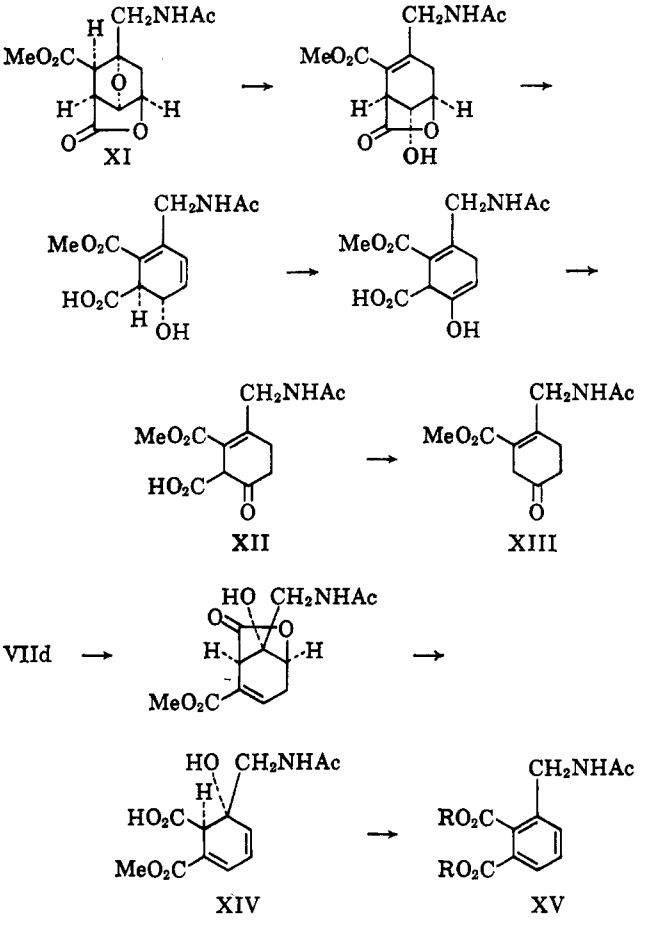


Xa, R = $CH_2CO_2Me$; R′ = H
b, R = $CH_2CO_2Me$; R′ = Me
c, R = $COCH_2Cl$; R′ = H
d, R = Ac; R′ = H

Attempted nitrosation of the amides VIIa and Xa under a variety of conditions, a reaction considered to be the first step in the transformation of the nitrogenous side chain into a carboxaldehyde unit, failed to yield N-nitroso compounds. Since the only need for the aldehyde function resided in its later use for the cleavage of its vicinal ether linkage, it was decided to rupture the oxide bridge by taking advantage of its location $\beta$ to carboxy or carbomethoxy groups in the unhomologated compounds. As a consequence, the reaction between the ester VIId and potassium *t*-butoxide was investigated. However, short exposure of VIId to the base merely led to the isomer VIIIa, while longer reaction time and a follow-up diazomethane treatment yielded an aromatic substance which on per-

(10) Although in anticipation of final structure proof, all further structural formulas will be based on VIa as the correct representation of the product of the Diels–Alder and halolactonization reactions.

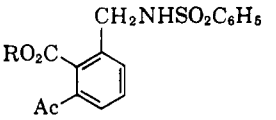
CHART I




manganate oxidation and diazomethane work-up produced trimethyl hemimellitate.

The aromatization of the ester VIId on extended base treatment constituted a further clue that we were working in the wrong isomer series from the point of view of a reserpine synthesis. The transformations (VIId–XV) based on structure VIId for the starting ester might have been expected indeed to yield aromatic products (of general structure XV).[11] A similar path is available to XI. However the conjugated diene from XI possesses a secondary alcohol which could readily undergo a base-catalyzed transformation leading to the nonaromatic product XIII or derivatives of XII. The tertiary alcohol XIV cannot undergo such a transformation and consequently seems more likely to lead to the observed, aromatization product. Thus an independent structure determination of the lactones VII became mandatory. (See Chart I.)

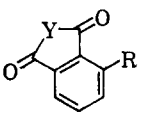
Aromatization of the ketone Xd, which could be prepared by hydrogenolysis of the chloro ketone Xc by potassium *t*-butoxide and subsequent diazomethane treatment, yielded a keto ester XVIa whose acid hydrolysis afforded a crystalline substituted benzoic acid XVIb. This acid appeared to be ideally suited for structure determination by synthesis. Furthermore, its being a 1,2,3-trisubstituted benzene system




XIVa, R = Me
b, R = H

suggested the use of derivatives of hemimellitic acid as starting compounds for the synthesis.[12]

With 4- or 7-acetylphthalimidine as initial goal, amination of the hemimellitic system was investigated. While treatment of molten hemimellitic anhydride (XVIIa) with gaseous ammonia has been reported to yield 3-carboxyphthalimide (XVIIb),[13] repetition of this experiment led to a mixture of XVIIb, its amide XVIIc, and monoammonium hemimellitate. 3-Carboxamidophthalimide (XVIIc) was identified by its alternate synthesis from the acid XVIIb on treatment with thionyl chloride and with ammonia as well as by its conversion into 3-cyanophthalimide (XVIId)[14] on treatment with phosphorus oxychloride. The identification of monoammonium hemimellitate rested on its spectral properties, its alternate preparation from a combination of aqueous equimolar solutions of hemimellitic acid and ammonium chloride, and its pyrolysis to 3-carboxyphthalimide (XVIIb).[15] Zinc–acetic acid reduction of 3-cyanophthalimide (XVIId), a reaction designed to produce precursors of our desired phthalimidines,[16] unfortunately afforded a difficultly separable mixture of products.[17]




XVIIa, R = $CO_2H$; Y = O
b, R = $CO_2H$; Y = NH
c, R = $CONH_2$; Y = NH
d, R = CN; Y = NH

The following alternate route of synthesis led to a phthalimidine series. 7-Hydroxymethylphthalide (XVIIIa)[12] was transformed into the chloromethyl derivative XVIIIb on thionyl chloride treatment and the latter, into the N-phthalimidomethyl compound XVIIIc on exposure to potassium phthalimide. Hydrazinolysis of the imide XVIIIc gave 7-hydroxymethylphthalimidine (XVIIId). Sarett oxidation of the latter yielded the aldehyde XVIIIe, whose interaction with methylmagnesium iodide afforded the carbinol XVIIIf. Oxidation of the alcohol with chromic acid in acetic acid produced 7-acetylphthalimidine (XVIIIg).

(11) The exact mode of dehydration of XIV is obscure, although, *inter alia*, three possible paths can be suggested: (a) solvolysis of the cyclohexadienol during the reaction or (b) upon acid work-up, or (c) formation of a cyclic anhydride by intramolecular methoxide displacement by the neighboring carboxylate salt, base-induced β-elimination of the hydroxy group and solvolysis of the resultant aromatic anhydride.

(12) *Cf.* E. Wenkert, D. B. R. Johnston, and K. G. Dave, *J. Org. Chem.*, **29**, 2534 (1964), for an extensive study of the chemistry of hemimellitic acid and the use of the aromatic acid in another structure elucidation by synthesis.

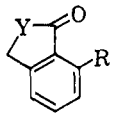
(13) C. Graebe and M. Leonhardt, *Ann.*, **290**, 217 (1896).

(14) This imide proved to be an interesting acidic substance. Passage of gaseous ammonia through a tetrahydrofuran solution of XVIId caused precipitation of an ammonium salt whose infrared spectrum in the carbonyl region was quite similar to that of potassium phthalimide. The salt reverted to XVIId on passage of nitrogen or air through its tetrahydrofuran suspension. This reversible salt formation could not be duplicated with phthalimide.

(15) The unusual insolubility of the salt in water and its amazing stability toward acid were reminiscent of similar properties exhibited by monopotassium hemimellitate.[13]

(16) *Cf.* J. H. Brewster, A. M. Fusco, L. E. Carosino, and B. G. Corman, *J. Org. Chem.*, **28**, 498 (1963), and references cited therein.

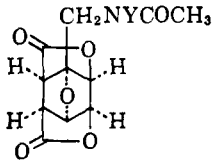
(17) Two crystalline $C_9H_6N_2O$ phthalimidines, m.p. 233–235° and 245–248°, respectively (C≡N 4.50 and C=O 5.90 μ), could be isolated. However, their structures were not determined.



XVIIIa, R = $CH_2OH$; Y = O
b, R = $CH_2Cl$; Y = O
c, R = $CH_2N(CO)_2C_6H_4$; Y = O
d, R = $CH_2OH$; Y = NH
e, R = CHO; Y = NH
f, R = CHOHMe; Y = NH
g, R = Ac; Y = NH

Treatment of the phthalimidine XVIIIg with base and benzenesulfonyl chloride yielded 2-acetyl-6-benzenesulfonamidomethylbenzoic acid (XVIb), identical in all respects with the aromatic degradation product of lactone Xd. This fact established the structures of all lactones as indicated in formulas VIIc, e, and f, VIIIb, and X and suggested strongly that the product of the Diels–Alder reaction of N-furfurylacetamide and maleic acid and subsequent halolactonization was the iodo lactone VIa, rather than the needed compound Va. While this structure proof appeared to foil our approach to reserpine, a residual opening for possible further progress has remained.

Base treatment of the iodo lactone VIa has been shown to lead to a dilactone XIXa. In an exploratory investigation the latter has been nitrosated and the resulting product (XIXb) has been changed to a diazo compound and thereafter to deaminated derivatives.[18] While this study has not been continued, the successful deamination of one of the lactones bodes well for the further pursuit of the reserpine synthesis along the general lines of the original hypothetical scheme.



XIXa, Y = H
b, Y = NO

## Experimental

**Iodo Lactone VIa.**—An ether (200 ml.) solution of 120 g. of furfurylamine was added with stirring to 150 g. of acetic anhydride in 150 ml. of ether at −20°. The solution was left standing for 18 hr. at room temperature and thereafter was distilled, to give 150 g. (85%) of N-furfurylacetamide, b.p. 135–137° (4 mm.).

A solution of 20 g. of maleic anhydride in 50 ml. of water was warmed 15 min. on the steam bath and combined with 20 g. of N-furfurylacetamide. After 68 hr. at room temperature, the solution was neutralized with 20% sodium hydroxide solution and combined with 250 ml. of 5% sodium bicarbonate solution. After cooling to 10° it was treated dropwise with 5 g. of iodine and 10 g. of potassium iodide in 30 ml. of water until the iodine color persisted for 15–20 min. The excess of iodine was destroyed with sodium thiosulfate and the solution was acidified. The precipitated product was isolated by filtration, dissolved in sodium bicarbonate solution, and reprecipitated by acidification. Yields of 35.7–40.1 g. of lactone VIa [m.p. 255°, unchanged on crystallization from methanol; infrared spectrum (Nujol) 3.02 (m) NH, C=O 5.64 (s), 5.89 (s), 6.20 (s), and 6.40 (s) $\mu$] were obtained.

*Anal.* Calcd. for $C_{11}H_{12}INO_6$: C, 34.65; H, 3.18. Found: C, 34.47; H, 3.23.

(18) The preparation of the compounds XIX and the preliminary study of the chemical behavior of the nitroso products are due to the efforts of Dr. E. W. Robb.

Treatment with diazomethane afforded the methyl ester (VIb): m.p. 208–209.4°; infrared spectrum (Nujol) NH 3.09 (m), C=O 5.60 (s), 5.80 (s), 6.09 (s), 6.18 (m), and 6.40 (s) $\mu$.

*Anal.* Calcd. for $C_{12}H_{14}NIO_6$: C, 36.45; H, 3.59. Found: C, 36.79; H, 3.84.

**Lactone VIIa.**—A solution of 11.4 g. of iodo lactone VIa in 150 ml. of water and 5.4 g. of sodium bicarbonate was shaken for 6 hr. with 3 g. of 5% palladium on charcoal in a hydrogen atmosphere at 50 p.s.i. It was then filtered, concentrated to 20 ml., and acidified. After standing in an ice–salt bath, the product precipitated and was removed by filtration: yield 6.0–7.1 g. (86–92%); m.p. 250–251°. Crystallization of the product from methanol gave VIIa: m.p. 250.6–251°; infrared spectrum (Nujol) NH 3.02 (m), C=O 5.64 (s), 5.88 (s), 6.20 (s), and 6.40 (s) $\mu$.

*Anal.* Calcd. for $C_{11}H_{13}NO_6$: C, 51.76; H, 5.15; N, 5.48. Found: C, 51.98; H, 5.26; N, 5.17.

Treatment of VIIa with ethereal diazomethane at 0° for no more than 0.5 hr. afforded needles of the methyl ester VIIb: m.p. 169–170° upon crystallization from methanol; infrared spectrum ($CHCl_3$) NH 2.90 (m) and 3.00 (w), C=O 5.60 (s), 5.78 (s), and 5.98 (s) $\mu$.

*Anal.* Calcd. for $C_{12}H_{15}NO_6$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.18; H, 5.72; N, 5.14.

**Isomerization of VIIb.**—A solution of 750 mg. of VIIb in 15 ml. of triethylamine and 15 ml. of acetonitrile was refluxed for 36 hr. under nitrogen and then evaporated under reduced pressure. The residue was crystallized from methanol giving 420 mg. of solid, m.p. 147–148°. Two more crystallizations afforded pure VIIIa: m.p. 149–150°; infrared spectrum ($CHCl_3$) NH 2.94 (m), C=O 5.62 (s), 5.78 (s), and 5.98 (s) $\mu$.

*Anal.* Calcd. for $C_{12}H_{15}NO_6$: C, 53.52; H, 5.61. Found: C, 53.49; H, 5.49.

**Amino Acid VIIb.**—A solution of 3 g. of VIIa in 112 ml. of 15% hydrochloric acid was refluxed for 1.5 hr. and then taken to dryness under reduced pressure. A small volume of water was added and the solution was again taken to dryness under reduced pressure; this process was repeated once more. The calculated amount of sodium bicarbonate (944 mg.) and 5 ml. of water were then added. The resultant suspension was cooled in ice, then filtered, giving 2.5 g. of solid, m.p. 260–262°. Recrystallization three times from water gave pure VIIb: m.p. 261–262°; infrared spectrum (Nujol) of the hydrated form showed bands for OH and NH at 2.90 (w), 3.00 (w), and 3.18 (w) and for C=O at 5.62 (s), 6.02 (m), 6.17 (s), 6.31 (s), and 6.58 (s) $\mu$.

*Anal.* Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.16; N, 6.57. Found: C, 50.84; H, 5.17; N, 6.40.

Acetylation of VIIb with acetic anhydride and water converted it to VIIa, identified by melting point, mixture melting point, and infrared spectrum.

**Benzenesulfonamide VIIc and Derivatives.**—The amino acid VIIb (800 mg.), 16 ml. of 5% sodium hydroxide solution, and 1.2 ml. of benzenesulfonyl chloride were shaken for 10 min. The basic solution was acidified and the resultant precipitate was isolated by filtration. Repeated crystallization from methanol–water did not improve the ill-defined melting point, ~123°, owing to the apparent hygroscopic character of the material. After drying at 78° under reduced pressure for 48 hr., the product, VIIc, had m.p. 185–186° and infrared spectrum (Nujol) of the hydrated form OH and NH 2.80 (m), 2.88 (m), and 3.00 (m), C=O 5.63 (s) and 5.78 $\mu$.

*Anal.* Calcd. for $C_{15}H_{15}NO_7S$: C, 50.98; H, 4.28; N, 3.96. Found: C, 50.78; H, 4.35; N, 3.99.

A suspension of VIIc in methanol was treated dropwise at 0° with an ether–tetrahydrofuran solution of diazomethane until the color of the last drop persisted. The solvent was immediately removed under reduced pressure and the residue was chromatographed on 40 times its weight of alumina. A trace of material was eluted with 1:1 chloroform–ether, while the main portion (80%) was eluted with 2:1 chloroform–ether up to straight chloroform. Crystallization from methanol gave VIIe: m.p. 160.2–161.5°; infrared spectrum ($CHCl_3$) NH 3.02 (w), C=O 5.61 (s) and 5.78 (s) $\mu$.

*Anal.* Calcd. for $C_{16}H_{17}NO_7S$: C, 52.30; H, 4.66; N, 3.81. Found: C, 52.20; H, 4.84; N, 3.74; 3.91.

When excess diazomethane was employed and the solution was allowed to stand *ca.* 1 hr. at 0°, nearly half of the material was eluted upon chromatography with 1:1 chloroform–ether. Crystallization from methanol gave pure VIIf: m.p. 157–158.5°; infrared spectrum ($CHCl_3$) C=O 5.61 (s) and 5.78 (s) $\mu$. The

mixture melting point with VIIe was depressed and their infrared spectra were different.

*Anal.* Calcd. for $C_{17}H_{19}NO_7S$: C, 53.53; H, 5.05; N, 3.67. Found: C, 53.89; H, 5.12; N, 3.67.

When excess diazomethane was employed and the solution was allowed to stand overnight, a new compound, VIIIb, was obtained upon evaporation of the solvent, m.p. 173–174°. It could also be obtained by refluxing VIIe in triethylamine–acetonitrile under nitrogen for 36 hr., and then treating the noncrystalline product with diazomethane in ether–methanol overnight. Repeated crystallization from methanol gave pure VIIIb: m.p. 175.5°; infrared spectrum ($CHCl_3$) C=O 5.61 (s) and 5.78 (s) $\mu$.

*Anal.* Calcd. for $C_{17}H_{19}NO_7S$: C, 53.5; H, 5.0; N, 3.6. Found: C, 53.19; H, 4.86; N, 3.37.

**Iodo Lactone IXa.**—Maleic anhydride (20 g.), 50 ml. of water, and 10 ml. of furan were stirred at room temperature for 72 hr., diluted to 84 ml., and treated with 16 g. of sodium bicarbonate. Subsequent treatment was identical with that employed in the formation of iodo lactone VIa (*vide supra*) and gave 15 g. of crude product. Crystallization from water gave pure IXa: m.p. 186.5–188°; infrared spectrum (Nujol) OH 2.82 (w), 2.84 (w), and 3.12 (w), C=O 5.67 (s) and 5.81 (s) $\mu$.

*Anal.* Calcd. for $C_8H_7IO_5$: C, 30.96; H, 2.57. Found: C, 30.91; H, 2.54.

**Lactone IXb.**—A solution of 13.5 g. of IXa, 8 g. of sodium bicarbonate, and 80 ml. of water was shaken with 2 g. of 5% palladium on charcoal in a hydrogen atmosphere at 50 p.s.i. for 5.5 hr. The solution was filtered, concentrated, and acidified to give 6 g. of solid, m.p. 183° (lit.[19] m.p. 174–175°), after isolation by filtration with infrared spectrum (Nujol) C=O 5.69 (s) and 5.85 (s) $\mu$.

Treatment of a methanolic solution of IXb with ethereal diazomethane afforded IXc: m.p. 149–150.5° after crystallization from methanol; infrared spectrum ($CHCl_3$) C=O 5.62 (s) and 5.88 (s) $\mu$.

*Anal.* Calcd. for $C_9H_{10}O_5$: C, 54.51; H, 5.10. Found: C, 54.44; H, 5.33.

**Derivatives of Acid IXb.**—A mixture of 1.1 g. of IXb and 10 ml. of thionyl chloride was stirred for 2 hr. at room temperature and then 1.5 hr. at 60°. The clear solution was evaporated under reduced pressure, the residue was dissolved in 5 ml. of tetrahydrofuran, and the solution was again taken to dryness under reduced pressure.

Treatment of 100 mg. of the acid chloride with methanol afforded IXc, m.p. 150.5°, after recrystallization from methanol. A mixture melting point with authentic IXc was undepressed and the infrared spectra were identical.

The acid chloride formed above, less 100 mg., was suspended in tetrahydrofuran and added slowly to a cold ether–tetrahydrofuran solution of diazomethane. After standing overnight, the solvent was evaporated and the residue was suspended in 25 ml. of refluxing methanol while silver oxide (from 1 g. of $AgNO_3$) was added over a 0.5-hr. period. The mixture was filtered, the solvent was evaporated under reduced pressure, and the residue was recrystallized from methanol to give 550 mg. of IXd: m.p. 143–144°; mixture melting point with IXc showing depression; infrared spectrum ($CHCl_3$) C=O 5.62 (s) and 5.78 (s) $\mu$.

*Anal.* Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.97; H, 5.84.

**Derivatives of Acid VIIc.**—A mixture of 800 mg. of VIIc and 10 ml. of thionyl chloride was stirred for 2 hr. at room temperature and 2 hr. at 60°. The clear solution was taken to dryness under reduced pressure, 5 ml. of benzene was added and then removed under reduced pressure, and the process was repeated once more. A solution of 150 mg. of acid chloride in methanol was evaporated to dryness under reduced pressure after 1 hr. at room temperature. The residue was chromatographed on 6 g. of alumina Ether–chloroform (3:5) eluted 105 mg. of crystalline solid, m.p. 157.5–159°. Recrystallizing from methanol afforded pure VIIe: m.p. 160.2–161.5°; mixture melting point with authentic VIIe undepressed; identical infrared spectra.

The acid chloride prepared above, less 100 mg., was dissolved in tetrahydrofuran and added slowly at 0° to a dry solution of diazomethane in ether–tetrahydrofuran. Fifteen minutes after the addition, the solvent was evaporated under reduced pressure and the residue ($C{=}N_2$ infrared band at 4.72 $\mu$) was suspended in 30 ml. of methanol at 50°. A small portion of silver oxide (from 1 g. of silver nitrate) was added, the suspension was then heated to reflux temperature, and the remaining silver oxide was added over 1 hr. The residue obtained, after filtration and evaporation under reduced pressure, was chromatographed on 24 g. of alumina. Ether–chloroform (1:3) eluted 422 mg. of solid which was recrystallized repeatedly from methanol to give pure Xa: m.p. 154.2–155°; infrared spectrum ($CHCl_3$) C=O 5.62 (s) and 5.79 (s) $\mu$.

*Anal.* Calcd. for $C_{17}H_{19}NO_7S$: C, 53.52; H, 5.22; N, 3.67. Found: C, 53.43; H, 5.22; N, 3.75.

Prior to elution of Xa, a different substance was eluted with 2:3 ether–chloroform. Repeated crystallization gave pure Xb: m.p. 126.5–127.5°; infrared spectrum ($CHCl_3$) C=O 5.61 (s) and 5.78 (s) $\mu$. It could also be prepared by exposing a methanol suspension of Xa to ethereal diazomethane overnight.

*Anal.* Calcd. for $C_{18}H_{21}NO_7S$: C, 54.67; H, 5.35; N, 3.93. Found: C, 54.48; H, 5.08; N, 3.83.

The diazo ketone was prepared as above from 1.07 g. of VIIc and, while still in solution, was treated with HCl gas. Upon evaporation to dryness, a residue was obtained which was recrystallized from methanol to give Xc: m.p. 166–167°; infrared spectrum (Nujol) NH 3.20 (m) C=O 5.62 (m), 5.72 (s), and 5.78 (m) $\mu$.

*Anal.* Calcd. for $C_{16}H_{16}ClNO_6S$: C, 49.79; H, 4.18; N, 3.63. Found: C, 50.02; H, 4.23; N, 3.88.

**Reactions of VIId with Base.**—A solution of 2.10 g. of VIId in 50 ml. of *t*-butyl alcohol containing 350 mg. of potassium was refluxed for 2 hr., carefully neutralized with concentrated hydrochloric acid, and treated with a solution of diazomethane. After evaporation of the solvents under reduced pressure, the resulting product was chromatographed on 70 g. of alumina. Elution with 1:3 chloroform–ether afforded 1.0 g. of an oil. (If refluxing was only carried out for 1–1.5 hr., VIIIa was obtained from the chromatography).

A mixture of 70 mg. of the oil, 160 mg. of $KMnO_4$, 116 mg. of KOH, and 10 ml. of water was heated on the steam bath for 1 hr. Excess permanganate was destroyed with methanol; the suspension was filtered and cooled yielding a crystalline precipitate. The precipitate was dissolved in hot water and a concentrated barium chloride solution was added. The resultant precipitate was isolated and dissolved in a large volume of hot water. Concentrated sulfuric acid was added until no more precipitation occurred. After filtration, concentration, and cooling, hemimellitic acid, m.p. 202–204° (lit.[13] m.p. 190–196°), was obtained. Upon treatment with ethereal diazomethane it was converted to trimethyl hemimellitate, m.p. 100.5° (lit.[13] m.p. 100–101°).

**Ketone Xd.**—A mixture of 407 mg. of Xc, 180 mg. of sodium bicarbonate, and 180 mg. of 5% palladium on charcoal in 25 ml. of tetrahydrofuran was shaken for 24 hr. in a hydrogen atmosphere at 50 p.s.i. and then filtered. The filtrate was evaporated under reduced pressure and the residue was crystallized from methanol. A total of 304 mg. of material was obtained which, upon repeated crystallization from methanol, gave pure Xd: m.p. 188–191° dec.; infrared spectrum (Nujol) NH 3.04 (w), C=O 5.63 (s) and 5.77 (s) $\mu$.

*Anal.* Calcd. for $C_{16}H_{17}NO_6S$: C, 54.70; H, 4.88; N, 3.99. Found: C, 54.90; H, 4.87; N, 3.97.

**Aromatization of Ketone Xd.**—A mixture of 48 mg. of Xd and 5 ml. of dry *t*-butyl alcohol was stirred under nitrogen until a homogeneous suspension was obtained. Then 0.4 ml. of 1.01 *M* potassium *t*-butoxide in *t*-butyl alcohol was added and the slurry was stirred at 80–90° under nitrogen for 3 hr. To this was added 0.3 ml. of 3 *M* hydrochloric acid and stirring and refluxing were resumed for 4 hr. The entire mixture was taken to dryness under reduced pressure, shaken with 3 ml. of 3 *M* hydrochloric acid, and extracted with chloroform. After drying and evaporation of the chloroform, 24 mg. of oil was obtained which was chromatographed on 0.6 g. of silicic acid. Elution with 3:2 ether–ligroin to 1:4 ether–chloroform afforded an oil which partially crystallized. There was obtained *ca.* 4 mg. of a solid, m.p. 190–197°. Repeated crystallized from acetone gave pure XVIb: m.p. 201–202°; infrared spectrum (Nujol) NH 3.01 (w), OH 3.12 (w), and C=O 5.71 (s) $\mu$; ultraviolet spectrum $\lambda_{max}$ 284 m$\mu$ (log $\epsilon$ 3.20).

*Anal.* Calcd. for $C_{16}H_{15}NO_3S$: C, 57.64; H, 4.53. Found: C, 57.57; H, 4.81.

**Reaction of Hemimellitic Anhydride and Gaseous Ammonia at 250°.**—Hemimellitic anhydride, from 938 mg. of hemimellitic acid, was heated to 250–260° and gaseous anhydrous ammonia was introduced below the surface of the liquid until it solidified.

(19) O. Diels and K. Alder, *Ann.*, **490**, 243 (1931).

The solid was extracted with 10% aqueous ammonium hydroxide. Drying of the insoluble residue by warming under reduced pressure gave 300 mg. of crude 3-carboxamidophthalimide (XVIIc), m.p. *ca.* 330° subl. Repeated crystallization from water afforded an analytical sample: m.p. 332–335° subl.; infrared spectrum (Nujol) 5.66 and 5.76 (imide C=O), and 5.93 (amide C=O) $\mu$.

*Anal.* Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.87; H, 3.45; N, 14.92.

The ammoniacal extracts obtained above were concentrated under reduced pressure and acidified, yielding 3-carboxyphthalimide (XVIIb). Crystallization from water afforded an analytical sample: m.p. 240–242° (lit.[13] m.p. 247°); infrared spectrum (Nujol) 5.65 (imide C=O) and 5.8–6.3 (imide and carboxyl C=O) $\mu$.

*Anal.* Calcd. for $C_9H_5NO_4$: C, 56.55; H, 2.64. Found: C, 56.43; H, 2.82.

Further concentration of the aqueous mother liquors afforded mixtures of 3-carboxyphthalimide and monoammonium hemimellitate. The latter compound was easily extracted from such mixtures with hot water. Repeated crystallization from water, afforded an analytical sample which, upon heating, lost water at *ca.* 180°, melted at *ca.* 190, but resolidified and melted again at *ca.* 235°. The infrared spectrum in Nujol showed a sharp peak at 5.80 and a broad complex band at 6.4 $\mu$.

*Anal.* Calcd. for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.62; H, 4.02; N, 6.01.

A sample of monoammonium hemimellitate was heated at 250° until it melted. Crystallization of the residue from water gave 3-carboxyphthalimide (XVIIb) identified by melting point, mixture melting point, and infrared spectral comparison with authentic material. Monoammonium hemimellitate could also be prepared by combining an aqueous solution of hemimellitic acid with an aqueous solution of 1 equiv. of ammonium hydroxide or 1 equiv. of ammonium chloride. In both cases the crystalline product was identical in all respects with the monoammonium hemimellitate obtained above.

**3-Carboxamidophthalimide (XVIIc) from 3-Carboxyphthalimide (XVIIb).**—A mixture of 5 ml. of thionyl chloride and 378 mg. of 3-carboxyphthalimide was refluxed for 4 hr. The solution was taken to dryness under reduced pressure and the residue, in tetrahydrofuran, was added dropwise to 10 ml. of ammonium hydroxide at 0° with rapid stirring. The mixture was concentrated under reduced pressure; the precipitate was collected, washed with ice-cold water, and dried, giving 284 mg. of crude 3-carboxamidophthalimide (XVIIc), m.p. and m.m.p. 331–333 subl. An infrared spectral comparison showed it to be identical with authentic material.

**3-Cyanophthalimide (XVIId).**—A mixture of 2.43 g. of 3-carboxamidophthalimide and 30 ml. of phosphorus oxychloride was stirred at 110–120° for 12 hr. After concentration to 10 ml. under reduced pressure and cooling, the excess phosphorus oxychloride was destroyed with ice-cold water. The solution was concentrated under reduced pressure and extracted repeatedly with chloroform. The extracts were combined, washed once with water, dried with magnesium sulfate, and evaporated under reduced pressure. Repeated crystallizations of the crude nitrile, 1.4 g., from methanol afforded an analytical sample: m.p. 232–233°; infrared spectrum (Nujol) 4.48 (C=N), 5.60 and 5.80 (imide C=O) $\mu$.

*Anal.* Calcd. for $C_9H_4N_2O_2$: C, 62.79; H, 2.34; N, 16.28. Found: C, 62.93; H, 2.47; N, 16.37.

**7-Chloromethylphthalide (XVIIIb).**—A solution of 40 mg. of 7-hydroxymethylphthalide (XVIIa)[12] in 0.2 ml. of thionyl chloride was allowed to stand for 68 hr. at room temperature. The solution was taken to dryness under reduced pressure and the resultant crystalline solid was crystallized from benzene to give XVIIIb: m.p. 108–110°; infrared spectrum (Nujol) C=O 5.70 (s) $\mu$.

*Anal.* Calcd. for $C_9H_7ClO_2$: C, 59.19; H, 3.86. Found: C, 59.45; H, 3.93.

**7-(2-Phthalimidomethyl)phthalide (XVIIIc).**—The chloromethylphthalide (XVIIIb) obtained above was dissolved in 2 ml. of dimethylformamide and stirred with *ca.* 100 mg. of potassium phthalimide at 105–115° for 2 hr. It was then taken to dryness under reduced pressure and the solid residue was extracted several times with chloroform. The extracts were combined and evaporated, and the residue, 78 mg., was crystallized repeatedly from chloroform to give XVIIIc: m.p. 251–252°; infrared spectrum (Nujol) C=O 5.65 (sh), 5.74 (s), and 5.86 (s) $\mu$.

*Anal.* Calcd. for $C_{17}H_{11}NO_4$: N, 4.78. Found: N, 4.72.

**7-Hydroxymethylphthalimidine (XVIIId).**—A mixture of 350 mg. of XVIIIc, 100 ml. of methanol, and 0.4 ml. of anhydrous hydrazine was stirred at 70° for 3 hr. The suspension was cooled to 0° and filtered; the residue was washed once with cold methanol and filtered. The combined filtrates were evaporated under reduced pressure and the residue was crystallized repeatedly from methanol to give XVIIId: m.p. 169–170°; infrared spectrum (Nujol) NH and OH 3.00 (w) and 3.2–3.4 (w) and C=O 5.95 (s) $\mu$.

*Anal.* Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56. Found: C, 66.15; H, 5.57.

**7-Formylphthalimidine (XVIIIe).**—A solution of 102 mg. of XVIIId in 2 ml. of pyridine was added to a solution of 105 mg. of $CrO_3$ in 2 ml. of pyridine. After standing 15 hr. it was poured into 10 ml. of water and the mixture was extracted repeatedly with chloroform. The extracts were dried and evaporated under reduced pressure, and the residue was chromatographed on 3 g. of alumina. Elution with 3:1 chloroform–ether led initially to fractions rich in product, then becoming progressively richer in starting material. Fractional crystallization of intermediate fractions from methanol afforded more product; *ca.* 30 mg. of material suitable for further reaction could thus be obtained. The remaining material was recycled through the oxidation. Repeated crystallization from methanol afforded pure XVIIIe: m.p. 211–215°; infrared spectrum (Nujol) C=O 5.89 (s) and 5.95 (s) $\mu$.

*Anal.* Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.95; H, 4.38; N, 8.57.

**7-($\alpha$-Hydroxyethyl)phthalimidine (XVIIIf).**—A solution of 59 mg. of XVIIIe in 10 ml. of tetrahydrofuran was added to methylmagnesium iodide (from 22 mg. of magnesium and 0.6 ml. of methyl iodide) in 1 ml. of ether under nitrogen, and then stirred at 80° for 2 hr. Water was added carefully and the mixture was taken to dryness under reduced pressure. The residue was taken up in dilute hydrochloric acid and extracted with chloroform. The extracts were washed with water, the water was extracted with chloroform, and the combined chloroform solutions were dried and evaporated to give 76 mg. of crude product. Repeated crystallization from water gave pure XVIIIf: m.p. 135–137°; infrared spectrum (Nujol) NH and OH 2.91 (w) and 3.15 (w) and C=O 5.97 (s) $\mu$.

*Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.27. Found: C, 67.67; H, 6.27.

**7-Acetylphthalimidine (XVIIIg).**—A solution of 1.8 mg. of chromium trioxide, 0.2 ml. of acetic acid, and 0.02 ml. of water was added to 5 mg. of XVIIIf in 0.1 ml. acetic acid. After 90 min., 3 ml. of water were added and the mixture was extracted exhaustively with chloroform. After drying and evaporation of the extract, 5.9 mg. of crude product was obtained. Crystallization from acetone gave 2.3 mg. of material (two crops). The mother liquors were recycled through the oxidation procedure. Repeated crystallization of the product from acetone gave pure XVIIIg: m.p. 204–205°; infrared spectrum (Nujol) NH 3.16 (w), C=O 5.90 (s) and 5.96 (s) $\mu$.

*Anal.* Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.60; H, 5.33.

**Benzenesulfonation of XVIIIg.**—A mixture of 5.2 mg. of XVIIIg and 0.5 ml. of 10% sodium hydroxide solution was heated at 120° for 2 hr. and then cooled. Benzenesulfonyl chloride (0.05 ml.) was added, and the mixture was shaken for 15 min. The basic homogeneous solution was extracted exhaustively with chloroform, leading to only a trace of neutral material. Upon acidification and extraction with chloroform, and thereafter drying and evaporation of the extract, a semisolid material was obtained. Careful washing with ice-cold chloroform gave crystals, m.p. 192–197°. Recrystallization from acetone gave XVIb, m.p. 198–200°, identified by mixture melting point and infrared spectrum.

**Dilactone XIXa.**—A mixture of 2.90 g. of VIa, 4.30 g. of anhydrous potassium carbonate, and 500 ml. of acetone was refluxed for 24 hr., filtered, and taken to dryness under reduced pressure. The residue was refluxed with 500 ml. of ethyl acetate, filtered, and concentrated to 30 ml. Upon cooling, 1.12 g. of XIXa crystallized. Repeated crystallization from methanol gave pure XIXa: m.p. 198–199°; infrared spectrum (Nujol) NH 3.15 (w), 3.29 (m), C=O 5.51 (m), 5.58 (s), 6.13 (m), and 6.30 (w) $\mu$.

*Anal.* Calcd. for $C_{11}H_{11}NO_5$: C, 52.17; H, 4.38; N, 5.53. Found: C, 51.81; H, 4.37; N, 5.57.

Treatment of 1.31 g. of XIXa in 40 ml. of acetic anhydride and 10 ml. of acetic acid at 0° over 0.5 hr. with 8.4 g. of sodium nitrite, storage overnight in the refrigerator, and pouring the mixture into 150 g. of ice led to a suspension. Filtration and successive washing with water and ether afforded 1.37 g. of crude XIXb. Attempts at recrystallization led to decomposition. Upon heating it decomposed violently at *ca.* 148°. Infrared spectrum (Nujol) showed no NH, C=O 5.55 (s) and 5.82 (s), and N=O 6.65 (m) μl Treatment of XIXb in methanol with sodium methoxide led, upon evaporation, to a yellow foam which exhibited an infrared spectrum in chloroform with an intense 4.82-μ band. In preliminary experiments, the diazo compound has been treated with several acidic reagents leading to evolution of nitrogen. Although incompletely characterized, the products showed no 4.82-μ band in their infrared spectra.

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# Reaction of Enol Ethers with Carbenes. VI.[1] Allylic Rearrangements of Sulfur Ylids[2]

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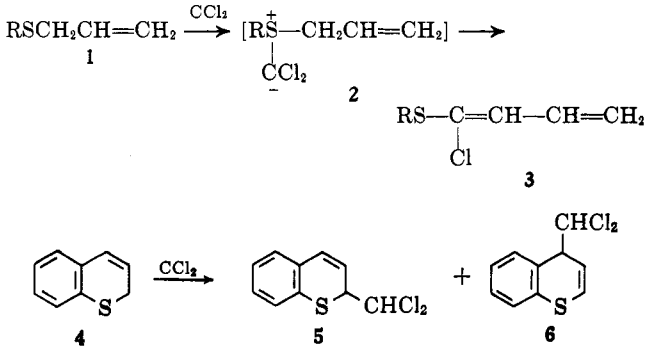
Evidence is presented for allylic rearrangements of sulfur ylids derived by reaction of ethyl trichloroacetate and sodium methoxide with noncyclic allyl sulfides. The reactions of α-, β-, and γ-methylallyl sulfides with ethyl trichloroacetate and sodium methoxide (dichlorocarbene) are discussed.

We previously observed[4-6] that dichlorocarbene, generated from ethyl trichloroacetate and sodium methoxide, reacts with open-chain allyl sulfides[4] (**1**) to give 1-chloro-1-substituted mercaptobutadienes (**3**) and with



cyclic allyl sulfides,[5,6] such as **4**, to give insertion products **5** and **6**. Sulfur ylids (**2**) were proposed as primary reaction products in these reactions; however, no definitive evidence for ylid formation from sulfides and dihalocarbenes has been noted. A study of the reactions of α-, β-, and γ-methylallyl sulfides with ethyl trichloroacetate and sodium methoxide, which is the subject of this report, has furnished evidence for the intermediate ylids **2** and has permitted definition of the probable mechanism of butadiene formation (**3**) to involve an allylic rearrangement of the ylid **2**. With appropriately substituted allylic sulfides, a duality of mechanism is observed.

(1) For the preceding article in this series, see W. E. Parham, R. W. Soeder, J. R. Throckmorton, K. Kuncl, and R. M. Dodson, *J. Am. Chem. Soc.*, **87**, 321 (1965).

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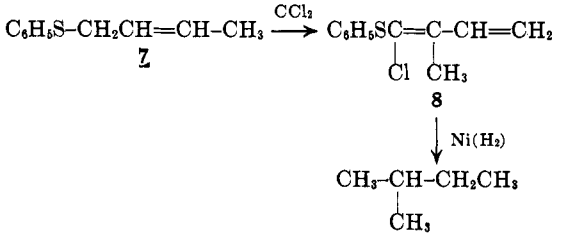
(4) W. E. Parham and S. H. Groen, *J. Org. Chem.*, **29**, 2214 (1964).

(5) W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, **83**, 4034 (1961).

(6) W. E. Parham, L. Christensen, S. H. Groen, and R. M. Dodson, *J. Org. Chem.*, **29**, 2211 (1964).

**Procedure. A. Reactions of γ-Methylallyl Sulfides.**—The reaction of γ-methylallyl phenyl sulfide (**7**), which contained ~6% (by v.p.c.) of the isomeric sul-



fide **11**, with ethyl trichloroacetate and sodium methoxide gave a 52% yield of product composed of >90% 1-chloro-2-methyl-1-phenylmercaptobutadiene (**8**) and <10% 1-chloro-1-phenylmercaptopentadiene-1,3 (**12**). The composition and infrared, ultraviolet, and n.m.r. spectra of the product (see Experimental) were consistent with the assigned structure **8**. Confirmation of the carbon structure of **8** was achieved by its reduction with Raney nickel to isopentane (derived from **8**) and *n*-pentane (derived from **12**) in the ratio of ~12 to 1.

Similar studies were made with *n*-butyl γ-methylallyl sulfide with comparable results (see Experimental). In this case the amount of contaminant (*n*-butyl α-methylallyl sulfide) in the starting sulfide was less. The ratio of derived isopentane to *n*-pentane was ~25 to 1.

**B. Reactions of β-Methylallyl Sulfides.**—The reaction of β-methylallyl phenyl sulfide (**9**) with ethyl trichloroacetate and sodium methoxide gave a 42% yield of 1-chloro-3-methyl-1-phenylmercaptobutadiene (**10**). The composition and infrared, ultraviolet, and n.m.r. spectra of the product (see Experimental) were consistent with the assigned structure **10**. The reaction