

Synthesis of some Sulfonium Salts and Ylides Containing the Isoxazole Nucleus (I)

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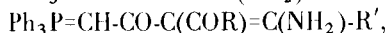
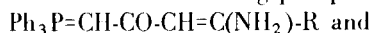
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Some dimethylisoxazolymethylsulfonium salts and the corresponding ylides were synthesized and their chemical behaviour studied. Dimethylsulfonium-5-isoxazolyl methylides (XIa,b) give 5-isoxazolylloxiranes (XIIa,d) and XIII when allowed to react with carbonyl compounds. Ring opening products from these oxiranes are also reported.

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As a result of the continuing interest in the chemistry of the isoxazole nucleus, we have studied the synthesis and behaviour of some isoxazole-substituted ylides. In two previous papers (2a,b), we reported the synthesis of the new and interesting phosphonium ylides

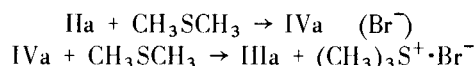


prepared by hydrogenolysis and treatment with base, respectively, from 5-isoxazolylalkyltriphenylphosphonium and 4-isoxazolylalkyltriphenylphosphonium salts.

We now wish to report the synthesis and chemical behaviour of some dimethylisoxazolymethylsulfonium salts and the corresponding ylides.

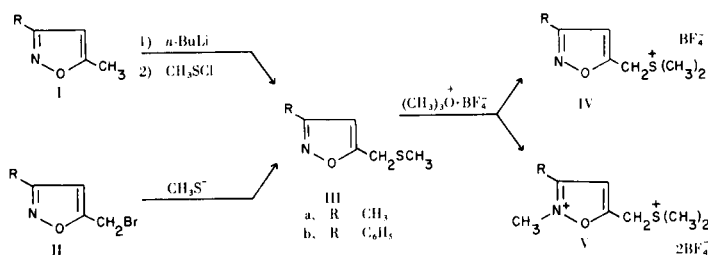
Synthesis of Dimethylisoxazolymethylsulfonium Salts.

Some attempts to prepare these sulfonium salts by the reaction of dimethylsulfide with the corresponding bromomethylisoxazoles did not give satisfactory results. As soon as it was formed, the salt was dealkylated by the nucleophilic dimethyl sulfide (3). Mixtures of methylthiomethylisoxazoles and trimethylsulfonium bromides were obtained as shown for the reaction of IIa:

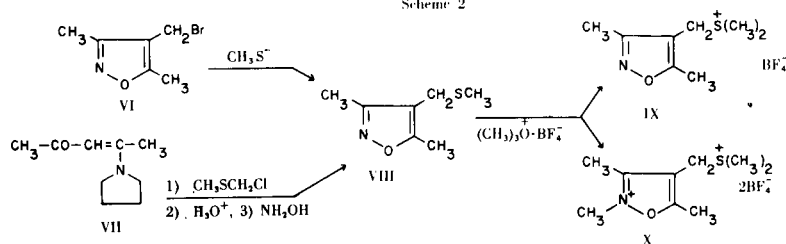


We therefore had to prepare the more stable fluoborates through the alkylation of methylthiomethylisoxazoles III

Scheme 1



Scheme 2



and VIII with Meerwein's reagent. Sulfides III and VIII were synthesized as reported in Schemes 1 and 2.

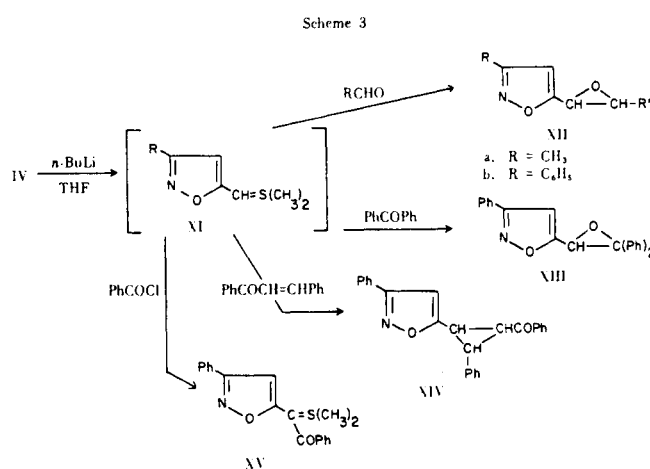
Sulfides IIIa,b were prepared in fair yield by the addition of methylsulfonyl chloride to a tetrahydrofuran solution of the anions prepared from 5-methylisoxazoles (Ia,b) with *n*-butyllithium (4). These same sulfides were also prepared in good yield from methyl mercaptan and 5-bromomethyl isoxazoles IIa,b, in basic media. Sulfide VIII was obtained from the reaction of methylmercaptan with the corresponding 4-bromomethylisoxazole (5). There is also a more rapid route to that compound starting from acetylacetone. From the alkylation of *N*-pyrrolidinoacetylacetone with methylchloromethyl sulfide, followed by acid hydrolysis of the product, one obtains 3-methylthiomethylacetylacetone. Upon heating in aqueous hydroxylamine, this forms sulfide VIII in an overall yield of 64%.

The following reaction of sulfides III and VIII with trimethyloxonium fluoborate to give the sulfonium salt requires some caution since the isoxazole nitrogen, though very slightly basic, may be alkylated by such a powerful alkylating agent. When the alkylation was performed in nitromethane by slowly adding a trimethyloxonium fluoborate solution (6) to an equimolar solution of isoxazolyl sulfide, the desired sulfonium salt was obtained in greater than 90% yield. On the other hand, when the sulfide solution was added to the fluoborate, a mixture of mono- and di-alkylated products was obtained instead. From a solution containing alkylating agent and sulfide in a 2-3 to 1 ratio, in nitromethane, there separated after some days the bis-salts Va,b and IX in yields from 70 to 90%. Sulfonium salts IVa,b and IX as well as bis-salts Va,b and X, are very stable white crystalline solids; spectroscopic and analytical data are reported in the experimental section.

Preparation and Reactivity of Dimethylsulfoniumisoxazolyl Methylides.

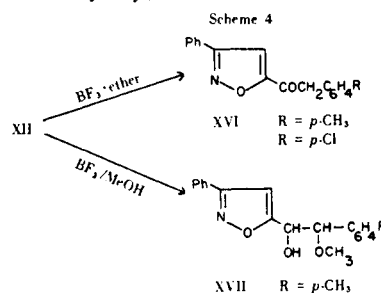
The ylides were generated from the corresponding salts suspended in tetrahydrofuran with *n*-butyllithium, under an inert atmosphere at temperature below -50° . Under these conditions, one obtains a dark red solution of the desired ylide which is stable for quite a while if held under an inert atmosphere at temperatures below -30° . When the solution is warmed to room temperature, it rapidly decolorizes as the ylide decomposes to give a complex mixture of products. Among the decomposition products of XIb, the major components have been identified as 3-phenyl-4-methylthiomethylisoxazole, product of a Sommelet-type rearrangement (7), and 3-phenyl-5-methylthiomethylisoxazole by comparison of the mixture with authentic samples by thin layer chromatography and nmr spectra.

The study of the reactivity of these ylides was performed using the 5-substituted isoxazoles because of their greater accessibility and stability; see Scheme 3. They react readily with aromatic aldehydes to give the corresponding *trans*-epoxides XII in yields ranging from 50 to 60%; they also react with ketones, but much more slowly. In the reaction of ylide XIb with benzophenone, epoxide XIII was formed in low yield (24%); it was contaminated with normal ylide decomposition products as well as unidentified side-products. The same ylide gave, on reaction with benzalacetophenone, only cyclopropane XIV, derived from a Michael addition of the ylide to the activated double bond. Finally, upon acylation with benzoyl chloride, stable ylide XV was formed.

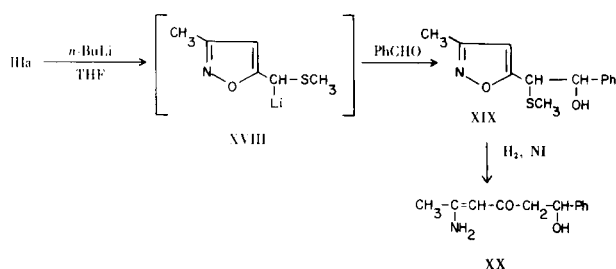


As shown by the decomposition products and reactions reported above (particularly the formation of cyclopropane from an α,β -unsaturated ketone), these sulfonium isoxazole ylides exhibit a reactivity typical for intermediately active sulfonium ylides such as dimethyl-oxosulfonium methylide and benzyloxosulfonium ylides (8).

Since we are also interested in the synthesis of polymethylene ketones (as intermediates in the biogenetic-like synthesis of some simple natural products), we wanted to see if some of the compounds discussed above could be used in this way; as already noted, the isoxazole ring can be considered as a protected β -diketone. Even though the results were not useful in this sense, we report them anyway, as follows.



Scheme 5



The first attempt was to prepare the open-chain sulfonium ylide $\text{Me}_2\text{S}=\text{CH}-\text{CO}-\text{CH}=\text{C}(\text{NH}_2)-\text{R}$ by catalytic hydrogenation of sulfonium salt IV followed by treatment with base, as we have already done with the corresponding phosphonium salts (2a,b). Unfortunately, during hydrogenation, the $\text{C}-\text{S}^+$ bond always underwent hydrogenolysis as well as the $\text{N}-\text{O}$ bond; and so the only isolated products were the β -iminoketones, $\text{CH}_3\text{COCH}=\text{C}(\text{NH}_2)\text{R}$. Upon reaction of boron trifluoride-etherate with epoxides XII in anhydrous ether, the ketones XVI were formed; while in methanol, the 1-hydroxy-2-methoxy compound XVII was obtained as a mixture of diastereomers, see Scheme 4. The isomeric ketone necessary for the preparation of the methylenetriketones was never formed in the course of these reactions.

Finally, with *n*-butyllithium in tetrahydrofuran at low temperature, sulfide IIIa formed the corresponding lithium salt XVIII, which is noticeably more stable than the anion prepared in the same way from 3,5-dimethylisoxazole. This salt reacts readily with benzaldehyde to give an almost quantitative yield of 1-(3-methylisoxazol-5-yl)-1-methylthio-2-hydroxy-2-phenylethane (XIX), as a one to one mixture of diastereomers. One of these was isolated in the pure state by chromatography on silica gel (see Experimental). Upon reduction of both isomers with hydrogen in the presence of Raney-nickel, 2-amino-4-oxa-6-oxy-6-phenyl-2-hexene (XX) was formed.

All reported structures are consistent with analytical and spectroscopic data, as reported in the Experimental.

EXPERIMENTAL

Infrared spectra (ir) were determined with Perkin Elmer model 137 "Infracord" spectrometer. Nuclear Magnetic Resonance (nmr) spectra were taken with a Varian Associates Model A60 or XL-100-15; chemical shifts (δ , ppm) were measured relative to tetramethylsilane as internal standard. Mass spectra (MS) were taken on a "Hitachi-Perkin Elmer RMU-6D" simple focusing spectrometer. Melting points were determined with a capillary apparatus and are uncorrected. Column chromatographies were performed on silica gel (0.05-0.20 mm, Merck, Darmstadt). Solutions were dried over sodium sulfate and solvent evaporations were performed *in vacuo*.

3-Methyl-5-methylthiomethylisoxazole (IIIa).

i) From 3,5-Dimethylisoxazole (Ia).

To a solution of Ia (9.7 g., 0.1 mole) in anhydrous tetrahydrofuran (100 ml.) cooled at -70° was added dropwise, under nitrogen, a solution of *n*-butyllithium in hexane (1.6 moles, 60 ml.). The yellow solution obtained after further stirring at -70° for 1 hour, was added dropwise to a freshly prepared solution of methylsulfenyl chloride (8.2 g., 0.1 mole) in tetrahydrofuran (50 ml.) cooled to -70° . After standing at room temperature for 1 hour, the reaction mixture was poured onto ice-water and extracted twice with ether. The ethereal extracts were washed with water, dried and the solvent evaporated. The crude product was purified by distillation through a 20 cm Vigreux column to give IIIa (5.1 g., 36%), b.p. $98-101^\circ$, 18 mm Hg; ir (liquid film): 3070, 1620, 1405, 1010, 900, 800 cm^{-1} ; nmr (deuteriochloroform): 2.10 (s, 3H, CH_3S); 2.25 (s, 3H, CH_3C); 3.71 (s, 2H, CH_2S) and 6.07 δ (s, 1H, =CH); MS: 143 (M^+), 96 m/e (M^+-MeS).

Anal. Calcd. for $\text{C}_6\text{H}_9\text{NOS}$: C, 50.3; H, 6.3; N, 9.8. Found: C, 50.0; H, 6.4; N, 9.7.

ii) From 5-Bromomethyl-3-methylisoxazole (IIa).

Methylmercaptan (8.4 g., 0.17 mole) was added in one portion to a solution of sodium methoxide (0.17 mole) in methanol (80 ml.) cooled to -15° . After 30 minutes stirring, a solution of IIa (28.4 g., 0.17 mole) in methanol (20 ml.) was added in portions so that the temperature did not rise above 0° . After standing at room temperature overnight, the solvent was removed and the residue taken up with ether. The organic layer was washed with water, dried and evaporated to dryness to give IIIa as a crude product. Distillation as reported above afforded pure IIIa (23.1 g., 95%) identified by spectral comparison with an authentic sample.

5-Methylthiomethyl-3-phenylisoxazole (IIIb).

This compound was obtained from IIb (10 g., 0.04 mole) according to the procedure previously described, m.p. $50-51^\circ$ from methanol (7.4 g., 90%); ir (nujol): 3130, 1605, 1470, 920, 780, 695 cm^{-1} ; nmr (deuteriochloroform): 2.15 (s, 3H, CH_3S); 2.75 (s, 2H, CH_2S); 6.48 δ (s, 1H, =CH); MS: 205 (M^+); 158 (M^+-MeS); 144 m/e ($\text{M}^+-\text{MeSCH}_2$).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{NOS}$: C, 64.4; H, 5.4; N, 6.8. Found: C, 64.1; H, 5.7; N, 6.5.

3,5-Dimethyl-4-methylthiomethylisoxazole (VIII).

i) From 3,5-Dimethyl-4-bromomethylisoxazole (VI).

Compound VIII was prepared, according to the procedure previously described, from VI (7 g., 0.037 mole). Compound VIII (5.3 g., 92%), b.p. $128^\circ/20$ mm Hg was obtained; nmr (deuteriochloroform): 2.01 (s, 3H, CH_3C); 2.26 (s, 3H, CH_3C); 2.34 (s, 3H, CH_3S); 3.42 δ (s, 2H, CH_2S); MS: 157 (M^+), 110 m/e (M^+-MeS).

Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{NOS}$: C, 53.5; H, 7.1; N, 8.9. Found: C, 53.8; H, 7.0; N, 9.0.

ii) From Acetylacetone.

A mixture of *N*-pyrrolidinoacetylacetone (15 g., 0.1 mole), chloromethyl-methyl sulfide (9.6 g., 0.1 mole) and benzene (100 ml.) was refluxed for 3 hours. After cooling, the reaction mixture was treated for 30 minutes with 10% sulfuric acid. Benzene was removed by distillation and the residue was taken up with ether. The ether layer was washed with saturated sodium bicarbonate solution and water, dried, and evaporated to dryness. The crude product was distilled through a Vigreux column. The

fraction, b.p. 112-115° at 760 mm Hg. was refluxed for 3 hours with a solution of hydroxylamine hydrochloride (8.4 g., 0.12 mole) and sodium carbonate (11.5 g., 0.13 mole) in water (80 ml.). After cooling, the reaction mixture was extracted with ether. The organic layer was washed with water, dried and the solvent removed. Fractional distillation of the crude material gave pure VIII (10 g., 64%), identified by spectral comparison with an authentic sample.

General Procedure for Preparation of Sulfonium Salts IV and IX.

To a solution of trimethyloxonium fluoborate (0.1 mole) in nitromethane (50 ml.) cooled to 0° was added dropwise, under nitrogen, a solution of sulfide III or VIII (0.1 mole) in nitromethane (20 ml.). The reaction mixture was allowed to stand overnight at -5°. The precipitate was filtered off, washed several times with nitromethane and recrystallized from methanol. The mother liquor (nitromethane) was evaporated to dryness and the residual-oil crystallized by slurry with methanol to afford additional product. Analytical samples were recrystallized twice with methanol, after decoloration by boiling with charcoal.

Dimethyl(3-methylisoxazol-5-yl)methylsulfonium Fluoborate (IVa).

This compound had m.p. 168-169°, 82%; ir (nujol): 3145, 1620, 1461, 1070-1020 (broad), 900 cm⁻¹; nmr (DMSO-d₆): 2.28 (s, 3H, CH₃C); 2.86 (s, 6H, Me₂S⁺); 4.88 (s, 2H, CH₂S); 6.66 δ (s, 1H, =CH).

Anal. Calcd. for C₇H₁₂NOSBF₄: C, 34.3; H, 4.9; N, 5.7. Found: C, 34.2; H, 5.1; N, 5.7.

Dimethyl(3-phenylisoxazol-5-yl)methylsulfonium Fluoborate (IVb).

This compound had m.p. 137-138°, 88%; ir (nujol): 1610, 1440, 1100-1040 (broad), 920, 780 cm⁻¹; nmr (DMSO-d₆): 2.95 (s, 6H, Me₂S⁺); 5.0 (s, 2H, CH₂S⁺); 7.36 δ (s, 1H, =CH).

Anal. Calcd. for C₁₂H₁₄NOSBF₄: C, 47.2; H, 4.6; N, 4.6. Found: C, 47.3; H, 4.6; N, 4.5.

Dimethyl(3,5-dimethylisoxazol-4-yl)methylsulfonium Fluoborate (IX).

This compound had m.p. 120-122°, 56%; ir (nujol): 1640, 1440, 1080-1020 (broad), 740 cm⁻¹; nmr (DMSO-d₆): 2.26 (s, 3H, CH₃C); 2.46 (s, 3H, CH₃C); 2.87 (s, 6H, Me₂S⁺); 4.53 δ (s, 2H, CH₂S⁺).

Anal. Calcd. for C₈H₁₄NOSBF₄: C, 37.1; H, 5.5; N, 5.4. Found: C, 37.2; H, 5.6; N, 5.3.

General Procedure for Preparation of Bis-salts V and X.

To a solution of trimethyloxonium fluoborate (0.25 mole) in nitromethane (100 ml.) was added under nitrogen a solution of the appropriate sulfide (0.1 mole) in nitromethane (50 ml.) at 0°. The bis-salt crystallized from the reaction mixture on standing for 2-3 days at -5°. Recrystallization from methanol afforded an analytical sample.

3-Methyl-5-(dimethylsulfoniummethyl)-N-methylisoxazolium Difluoroborate (Va).

This compound had m.p. 124-125°, 85% yield; ir (nujol): 3144, 1620, 1440, 1420, 1080-1030 (broad), 850 cm⁻¹; nmr (DMSO-d₆): 2.67 (s, 3H, CH₃C); 2.98 (s, 6H, Me₂S⁺); 4.30 (s, 3H, CH₃N⁺); 5.10 (s, 2H, CH₂S⁺); 7.45 δ (s, 1H, =CH).

Anal. Calcd. for C₈H₁₅NOSB₂F₈: C, 27.7; H, 4.4; N, 4.0. Found: C, 27.9; H, 4.5; N, 3.8.

3-Phenyl-5-(dimethylsulfoniummethyl)-N-methylisoxazolium Difluoroborate (Vb).

This compound had m.p. 150°, 92% yield; ir (nujol): 3110, 1620, 1460, 1100-1080 (broad), 1000, 840, 770 cm⁻¹; nmr (DMSO-d₆): 3.03 (s, 6H, Me₂S⁺); 4.46 (s, 3H, CH₃N⁺); 5.20 (s, 2H, CH₂S⁺); 7.96 δ (s, 1H, =CH).

Anal. Calcd. for C₁₃H₁₇NOSB₂F₈: C, 38.2; H, 4.2; N, 3.4. Found: C, 38.1; H, 4.1; N, 3.4.

3,5-Dimethyl-4-(dimethylsulfoniummethyl)-N-methylisoxazolium Difluoroborate (X).

This compound had m.p. 159-160°, yield 72%; ir (nujol): 1632, 1580, 1440, 1070-1040 (broad), 820 cm⁻¹; nmr (DMSO-d₆): 2.65 (s, 3H, CH₃C); 2.72 (s, 3H, CH₃C); 2.95 (s, 6H, Me₂S⁺); 4.25 (s, 3H, CH₃N⁺); 4.72 δ (s, 2H, CH₂S⁺).

Anal. Calcd. for C₉H₁₇NOSB₂F₈: C, 30.0; H, 4.8; N, 3.9. Found: C, 30.1; H, 4.7; N, 3.8.

General Procedure for Preparation of Sulfonium Ylides XI and Reaction with Electrophiles.

To a mixture of the appropriate sulfonium salt (0.1 mole) in anhydrous tetrahydrofuran cooled to -70° was added dropwise under nitrogen an equimolar amount of 1.6 M solution of *n*-butyllithium in hexane. The red solution was stirred at -70° for an additional hour. A solution of the appropriate electrophile (0.1 mole) in dry tetrahydrofuran (20 ml.) was then added at such a rate that the temperature was kept under -70°. After 20 minutes, the mixture was allowed to stand at room temperature for 1 hour. The solvent was removed and the residue taken up with a 1/1 mixture of ether/water. The organic layer was separated, washed with saturated ammonium chloride solution and water, then dried and evaporated. Generally the crude product was purified by column chromatography, using as eluent a hexane-ether (80:20) mixture. The following compounds were obtained.

1-(3-Methylisoxazol-5-yl)-2-(4-tolyl)epoxyethane (XIIa).

This compound had m.p. 61° from methanol, 60% yield; ir (nujol): 3130, 1615, 1415, 1000, 815 cm⁻¹; nmr (deuteriochloroform): 2.30 (s, 3H, CH₃); 2.35 (s, 3H, CH₃); 3.94 and 4.19 (doublets, 2H, J = 2 Hz, CH-CH); 6.15 (s, 1H, =CH); 7.20

δ (m, 4H, aromatics); MS: 215 (M⁺); 186 (M⁺-CHO); 172 [M⁺-(CHO + Me)]; 158 m/e [M⁺-(CHO + CO)].

Anal. Calcd. for C₁₃H₁₃NO₂: C, 72.5; H, 6.1; N, 6.4. Found: C, 72.8; H, 5.9; N, 6.5.

1-(3-Phenylisoxazol-5-yl)-2-(4-tolyl)epoxyethane (XIIb).

This compound had m.p. 130° from benzene-hexane, 62% yield; ir (nujol): 3115, 1610, 1450, 1410, 950, 995, 810 cm⁻¹; nmr (deuteriochloroform): 2.37 (s, 3H, CH₃C); 4.03 and 4.26 (doublets, J = 2 Hz, CH-CH); 6.62 δ (s, 1H, =CH); MS: 277

(M⁺); 248 (M⁺-CHO); 220 m/e [M⁺-(CHO + CO)].

Anal. Calcd. for C₁₈H₁₅NO₂: C, 78.0; H, 5.4; N, 5.1. Found: C, 78.1; H, 5.3; N, 5.1.

1-(3-Phenylisoxazol-5-yl)-2-(4-methoxyphenyl)epoxyethane (XIIc).

This compound had m.p. 124° (benzene-hexane), 51% yields; ir (nujol): 3130, 1610, 1465, 1470, 1450, 1250, 1170, 1030, 820 cm⁻¹; nmr (deuteriochloroform): 3.80 (s, 3H, OCH₃); 4.03 and 4.23 (doublets, J = 2 Hz, CH-CH); 6.60 δ (s, 1H, =CH);

MS: 293 m/e (M⁺).

Anal. Calcd. for C₁₈H₁₇NO₃: C, 73.7; H, 5.1; N, 4.8.

Found: C, 73.9; H, 5.1; N, 4.9.

1-(3-Phenylisoxazol-5-yl)-2-(4-chlorophenyl)epoxyethane (XIId).

This compound had m.p. 134° (benzene-hexane), 47% yield; ir (nujol): 3050, 1610, 1490, 1460, 1440, 1080, 1010, 840 cm^{-1} ; nmr (deuteriochloroform): 3.98 and 4.25 (doublets, $J = 2$ Hz, CH-CH); 6.61 δ (s, 1H, =CH); MS: 297 (M^+); 268 (M^+ -CHO);

262 (M^+ -Cl); 240 [M^+ -(CHO + CO)]; 234 m/e [M^+ -(Cl + CO)].

Anal. Calcd. for $C_{17}H_{12}ClNO_2$: C, 68.9; H, 4.1; N, 4.7. Found: C, 68.7; H, 3.8; N, 4.7.

1-(3-Phenylisoxazol-5-yl)-2,2-diphenylepoxyethane (XIII).

This compound had m.p. 122° (ethanol), 24% yield; ir (nujol): 1610, 1440, 955, 910, 765, 700 cm^{-1} ; nmr (deuteriochloroform): 4.50 (s, 1H, CH-O); 5.78 δ (s, 1H, =CH); MS: 339 (M^+); 310 (M^+ -CHO); 194 [$(C_6H_5)_2C=CO^+$]; 165 m/e ($C_{13}H_9^+$).

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.7; H, 5.2; N, 4.3. Found: C, 81.0; H, 5.1; N, 4.2.

1-(3-Phenylisoxazol-5-yl)-2-benzoyl-3-phenylcyclopropane (XIV).

This compound had m.p. 109° (benzene-hexane), 52% yield; ir (nujol): 1660, 1610, 1450, 1400, 1115, 1015, 770, 745, 700 cm^{-1} ; nmr (deuteriochloroform): 3.20-4.20 δ (multiplet for CH-CH); MS: 365 (M^+); 260 m/e (M^+ - C_6H_5CO).

Anal. Calcd. for $C_{25}H_{19}NO_2$: C, 82.2; H, 5.2; N, 3.8. Found: C, 81.9; H, 5.0; N, 3.7.

Dimethylsulfoniumbenzoyl(3-phenylisoxazol-5-yl)methylide (XV).

This compound had m.p. 172° (benzene-hexane), 28% yield; ir (nujol): 3100, 1530, 1395, 1330, 765, 720 cm^{-1} ; nmr (deuteriochloroform): 2.92 (6H, Me_2S); 7.2-7.7 δ (multiplet); MS: 323 (M^+); 308 m/e (M^+ -Me).

Anal. Calcd. for $C_{19}H_{17}NO_2S$: C, 71.1; H, 5.3; N, 4.3. Found: C, 71.1; H, 5.3; N, 4.3.

3-Phenyl-5-(4-tolyl)acetylisoaxazole (XVIa).

A mixture of epoxide XIId (0.5 g., 2.5 mmoles) and boron trifluoride etherate (2.3 ml.) was stirred at room temperature for 2 hours. The reaction mixture was poured in water and extracted with ether. The organic layer was washed with saturated sodium bicarbonate solution and with water, then dried and evaporated to dryness. The residue was crystallized from ethanol to afford XVIa (0.25 g., 50%), m.p. 128°; ir (nujol): 1680, 1510, 1430, 1265, 925, 770, 725 cm^{-1} ; nmr (deuteriochloroform): 2.30 (s, 3H, CH_3); 4.22 δ (s, 2H, CH_2CO); MS: 277 (M^+), 248 (M^+ -CHO), 220 [M^+ -(CO + CHO)], 172 (M^+ - $CH_2C_6H_4CH_3$), 144 (M^+ - $COCH_2C_6H_4CH_3$), 105 m/e ($CH_2C_6H_4CH_3^+$).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 78.0; H, 5.5; N, 5.1. Found: C, 78.3; H, 5.1; N, 4.9.

3-Phenyl-5-(4-chlorophenyl)acetylisoaxazole (XVIb).

This compound was prepared according to the procedure described above, m.p. 175° from ethanol, 67% yield; ir (nujol): 1690, 1470, 1435, 1180, 935, 810, 775 cm^{-1} ; nmr (deuteriochloroform): 4.26 (s, 2H, CH_2CO); 7.23 δ (s, 1H, =CH); MS: 297 (M^+), 268 (M^+ -CHO), 240 [M^+ -(CHO + CO)], 172 (M^+ - $CH_2C_6H_4Cl$), 144 (M^+ - $COCH_2C_6H_4Cl$) 125 m/e ($CH_2C_6H_4Cl^+$).

Anal. Calcd. for $C_{17}H_{12}ClNO_2$: C, 70.2; H, 7.4; N, 6.8. Found: C, 70.0; H, 7.2; N, 6.6.

1-(3-Phenylisoxazol-5-yl)-1-hydroxy-2-(4-tolyl)-2-methoxyethane (XVII).

A mixture of XIId (0.28 g., 1 mmoles) boron trifluoride etherate (5 ml.) and methanol (25 ml.) was refluxed for 30 minutes. After cooling, the reaction mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated sodium bicarbonate solution and with water, dried and the solvent evaporated. Thin layer chromatography on silica gel (eluent: hexane-ether, 70-30) showed that the residue consisted of two products in one to one ratio. The compounds were separated with preparative thin layer chromatography to afford the two possible diastereoisomer for XVII.

a)

Isomer m.p. 112° from ethanol ($R_f = 0.54$; ether-hexane 70-30); ir (nujol): 3120, 1470, 1405, 1135, 1085, 770 cm^{-1} ; nmr (deuteriochloroform): 2.31 (s, 3H, CH_3C); 3.30 (s, 3H, CH_3O); 3.44 (d, $J = 4$ Hz, 1H, OH); 4.50 (d, $J = 7$ Hz, 1H, CH-OMe); 4.90 (dd, $J_{H,OH} = 4.0$ Hz, $J_{H,CH} = 7.0$ Hz, 1H, CH-OH); 6.44 δ (s, 1H, =CH); MS: 310 ($M+1$)⁺; 135 m/e ($CH_3C_6H_4CH=OCH_3$)⁺.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5. Found: C, 74.0; H, 6.4; N, 4.6.

b)

Isomer m.p. 92-95° from ethanol ($R_f = 0.46$; ether-hexane, 70-30); ir (nujol): 3420, 3120, 1465, 1445, 1110, 1085, 770 cm^{-1} ; nmr (deuteriochloroform): 2.28 (s, 3H, CH_3C); 3.13 (d, $J = 6.0$ Hz, OH); 3.28 (s, 3H, CH_3O); 4.58 (d, $J = 5.0$ Hz, 1H, CH-OMe); 5.04 (dd, $J_{H,CH} = 5.0$ Hz, $J_{H,OH} = 6.0$ Hz, CH-OH); 6.40 δ (s, 1H, =CH); MS: 310 ($M+1$)⁺ m/e.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5. Found: C, 73.9; H, 6.1; N, 4.5.

1-(3-Phenylisoxazol-5-yl)-1-methylthio-2-phenyl-2-hydroxyethane (XIX).

To a solution of IIIa (4.3 g., 0.03 mole) in dry tetrahydrofuran (50 ml.) was added a 1.8 M solution of *n*-butyllithium in hexane (1.6 ml., 0.03 mole) under nitrogen at -50°. After 20 minutes at this temperature, the mixture was added in one portion to a solution of benzaldehyde (3.2 g., 0.03 mole) in tetrahydrofuran (50 ml.) cooled to -70°. The mixture was allowed to reach ambient temperature and then poured into water. The aqueous layer was acidified with 10% hydrochloric acid and extracted three times with ether. The combined organic layers were dried and the solvent removed to give a crude residue (7.1 g., 95% yield). Thin layer chromatography on silica gel (hexane-ether 70-30) and nmr spectrum showed it to consist of two products in a one to one ratio. The compound melting at 117-118° (benzene-hexane) was obtained in a pure state by column chromatography on silica gel (hexane-ether, 90-10); ir (nujol): 3320, 1600, 1445, 1055, 1005, 760, 700 cm^{-1} ; nmr (deuteriochloroform): 2.08 (3H, s, CH_3S); 2.18 (s, 3H, CH_3C); 3.30 (d, $J = 3.0$ Hz, 1H, OH); 4.07 (d, $J = 8.0$ Hz, 1H, CHS); 5.03 (dd, $J_{CH,OH} = 3.0$ Hz, $J_{H,CH} = 8.0$ Hz, CHOH); 5.82 δ (s, 1H, =CH); MS: 249 (M^+); 143 (M^+ - C_6H_5CHO); 128 (M^+ - C_8H_9O) 107 m/e (C_6H_5CHOH)⁺.

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.6; H, 6.1; N, 5.6. Found: C, 62.4; H, 6.2; N, 5.7.

A second compound was obtained by elution with hexane-ether mixture (80-20) and was contaminated by the compound melting at 117-118°. Repeated crystallization with benzene or ethanol did not give a sample of high purity, m.p. 90-96°; nmr (deuteriochloroform): 1.95 (s, 3H, CH_3S); 2.22 (s, 3H, CH_3C); 2.95 (d, $J = 4.5$ Hz, OH); 4.15 (d, $J = 6$ Hz, 1H, CHSM);

5.08 (dd, $J_{\text{H,OH}} = 4.5$ Hz, $J_{\text{H,CH}} = 6.0$ Hz, 1H, *CHOH*); 6.05 δ (s, 1H, =CH).

2-Amino-6-hydroxy-6-phenyl-2-hexen-4-one (XX).

A solution of XIX (2.2 g., 0.01 mole) in ethanol (80 ml.) was hydrogenated at room temperature, at 2 atmospheres, in a Parr apparatus in the presence of Raney nickel (0.2 g.) for two hours. The catalyst was filtered off and the solvent removed. The residue was crystallized from benzene-hexane to give XX (1.2 g., 58% yield), m.p. 116-119°; ir (nujol): 3330, 3190, 1600, 1525, 1150, 1050, 765 cm^{-1} ; nmr (deuteriochloroform): 1.88 (s, 3H, $\text{CH}_3\text{C}=\text{}$); 2.63 (d, $J = 6.0$ Hz, 2H, CH_2CO); 4.98 (s, 1H, =CHCO); 5.08 (t, $J = 6.0$ Hz, 1H, *CHOH*); 4.35, 5.65 and δ 8.45 (broad exchangeable with deuterium oxide, OH and NH_2); MS: 205 m/e (M^+).

Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{NO}_2$: C, 70.2; H, 7.2; N, 6.8. Found: C, 70.1; H, 7.3; N, 6.8.

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