Synthesis of Various Heterocyclic Compounds by Use of Diazomethane

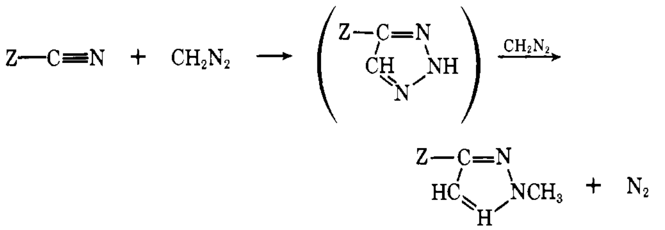
JOHN M. STEWART,[1] ROBERT L. CLARK, and PAUL E. PIKE
Department of Chemistry, University of Montana, Missoula, Mont. 59801

A number of new heterocyclic compounds have been prepared by reactions of diazomethane with several types of multiple linkages. Reactions included were those with cyano groups in compounds having electron-attracting substituents on a carbon adjacent to the cyano group to form 2-methyl-4-substituted-*vic*-triazoles; with the carbon-nitrogen double bond in Schiff bases to form 1,5-disubstituted-1,2,3-triazolines; with the carbonyl group in perchlorocarbonyl compounds with elimination of nitrogen to form epoxides; with 1- and 4-vinyl pyridines to give the corresponding pyrazolinyl pyridine; and with unsaturated sulfones to give structures containing pyrazoline rings or a pyrazoline ring fused to another ring.

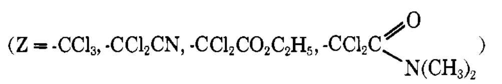
In connection with a program of testing a variety of heterocyclic structures for different types of physiological activity, a number of new compounds have been prepared by the reactions of diazomethane with several types of multiple linkages.

PROCESSES

Reaction of Diazomethane with Cyano Groups. Earlier reports (*3–5*) described the addition reaction of diazomethane with cyano groups having electron-withdrawing groups attached directly to the cyano group, e.g., —Cl, —Br, and —CN, to form substituted triazoles. In our work a number of compounds were used in which a carbon atom adjacent to the cyano group was bonded to at least two chlorine atoms:



I

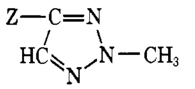


$(Z = \text{-}CCl_3, \text{-}CCl_2CN, \text{-}CCl_2CO_2C_2H_5, \text{-}CCl_2C(=O)N(CH_3)_2)$

Yields, physical properties, and elemental analysis data for these 2-methyl-4-substituted-*vic*-triazoles are listed in Table I. In no case was the simple intermediate addition compound isolated regardless of the ratio of reactants or the conditions used. The rate of the secondary methylation reaction was obviously faster than the initial addition, and nitrogen was evolved continuously as diazomethane was added to the nitrile. Although three tautomers are possible for the intermediate and thus three isomeric structures for I, only one product isomer appeared to be present in any significant amount in the four cases studied, on the basis of gas chromatography or thin layer chromatography analysis of samples. The isomer structure I as shown is tentative and based only on infrared spectral evidence in the lack of an absorption band characteristic of the —N=N— group at around 1550 cm^{-1} which would have indicated one of the other two isomer structures and in the presence of a weak absorption band at 1625–1650 cm^{-1}, ascribed to the aromatic C=N stretching frequency.

The apparent formation of only one triazole isomer in significant amount is in contrast to the work of Pedersen (*3*) who isolated and characterized all three possible *N*-methylbromo-*vic*-triazoles from the reaction of excess diazomethane with cyanogen bromide.

Table I. 2-Methyl-4-Substituted -*vic*-Triazoles[a]



Z	Yield, %	Bp, ° C, mm	Mp, ° C	n_D^{25}
Cl_3C-	80	52–53 (0.3)	28–30	1.5170
$NCCCl_2$-	65–80	52–54 (0.1)		1.5007
$C_2H_5O_2CCCl_2$-	80	96–98 (0.4)		1.4930
$(CH_3)_2N\overset{O}{\overset{\|}{C}}CCl_2$-	56	130–134 (0.3)	87–88	

[a] Elemental analyses (C, H, N) for the new compounds reported here, in agreement with theoretical values, have been obtained and submitted for review.

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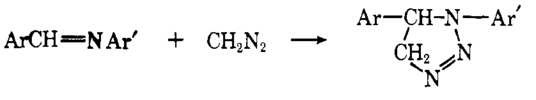
[1] To whom correspondence should be addressed.

Nuclear magnetic resonance spectra of these compounds showed only two sharp singlets, one for the triazole ring proton at δ 7.7–8.0 and one of three times that intensity for the protons of the *N*-methyl group at δ 4.1–4.3.

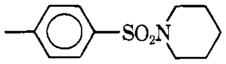
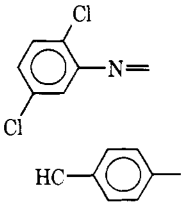
Reaction of Diazomethane with Schiff Bases. Conditions for the effective addition of diazomethane to the carbon-nitrogen double bond in Schiff bases have been described earlier (*2*), and these conditions were followed in this work. A number of new Schiff bases were prepared and their physical properties and elemental analysis data are shown in Table II. Most of these compounds reacted slowly with diazomethane over a period of several days to give reasonably good yields of 1,5-disubstituted-1,2,3-triazolines:



II

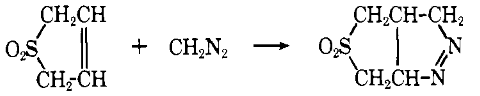
Best yields were obtained when both aromatic rings of the Schiff base had electron-withdrawing substitutents ortho or para to the imine group. The indicated placement of the triazoline ring double bond between nitrogen atoms 2 and 3 was substantiated by infrared absorption at 1550–1600 cm^{-1} in all of these products, characteristic of the N=N group and absent in the spectrum of the original Schiff base. Nuclear magnetic resonance spectra of these compounds also fitted the structure shown, the three protons of the triazoline ring appearing as a multiplet within the range of δ 4.2–5.5. Table III lists data for the new triazolines.

Table II. Schiff Bases, Ar(R)CH=N—Ar′[a]

Ar(R)	Ar′	Mp, °C (recryst. solvent)
Phenyl	4-Carbethoxyphenyl	45–46[b] (Cyclohexane)
4-Chlorophenyl	4-Carbethoxyphenyl	117–118 (Abs ethanol)
2,4-Dichlorophenyl	4-Carbethoxyphenyl	90–91 (Ether)
2,4-Dichlorophenyl	2-*N*,*N*-dimethylcarboxamidophenyl	91.5–92.5 (Cyclohexane)
2-Furanyl	4-Carbethoxyphenyl	44–46 (Ether)
4-Chlorophenyl		143–144 (Benzene + cyclohexane)
4-Chlorophenyl	4-*N*,*N*-dimethylsulfonamidophenyl	161–162 (Benzene + cyclohexane)
4-Chlorophenyl	4-*N*,*N*-diethylsulfonamidophenyl	107–109 (Cyclohexane)
2-Furanyl	4-*N*,*N*-dimethylsulfonamidophenyl	145–146 (Benzene)
	2,5-Dichlorophenyl	230 (Benzene)
Epoxyethyl	2-Carbethoxyphenyl	112–112.5 (Ether-benzene)

[a] Elemental analyses (C, H) for the new compounds reported here in agreement with theoretical values have been obtained and submitted for review. [b] Lit 46°.

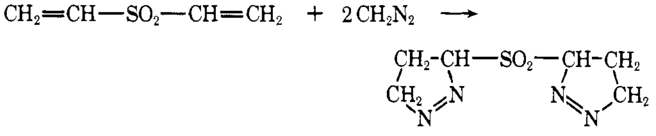
Reaction of Diazomethane with Unsaturated Sulfones. The unconjugated cyclic sulfone, butadiene sulfone, reacted very slowly with diazomethane in ether over a period of several days to give fair yields of 7-dioxythia-2,3-diazabicyclo-[3.3.0]oct-2-ene:



III

The yield could be improved somewhat by using dioxane containing 5% water as solvent for the unsaturated sulfone and adding the ether–diazomethane solution to this. Presence of the N=N grouping in the ring system was confirmed by infrared absorption at 1550 cm^{-1}.

The α,β-unsaturated sulfone, divinyl sulfone, reacted rapidly with excess diazomethane in ether solution, the product bis(1-pyrazolin-3-yl)sulfone (IV) crystallizing from solution as it formed in 100% crude yield.

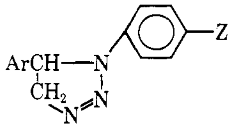


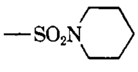
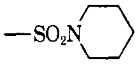
IV

Although the product shown indicates a Δ^1 structure for the pyrazoline rings, the infrared spectrum indicated that at least some Δ^2 structure was present, as evidenced by both —NH absorption at 3400 cm^{-1} and N=N absorption at 1550 cm^{-1}. A range of several degrees in the melting point of the recrystallized analytical sample also indicated the presence of isomers.

Reaction of Diazomethane with Perchloro Carbonyl Compounds. The addition of diazomethane to an ether solution of hexachloroacetone resulted in continual vigorous evolu-

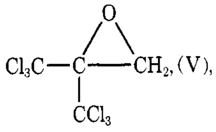
Table III. 1,5-Disubstituted-1,2,3-triazolines[a]



Ar	Z	Yield,[b] %	Mp, °C (Solvent)
Phenyl	Carbethoxy	54.6	125–126 (Abs ethanol)
4-Chlorophenyl	Carbethoxy	86.0	127–129 (Ether)
2,4-Dichlorophenyl	Carbethoxy	76.0	84–86 (Ether)
2-Furanyl	Carbethoxy	45.0	111—113 (Ether)
2-Chlorophenyl	*N*,*N*-dimethylsulfonamido	65.0	142–143 (Ethyl acetate)
4-Chlorophenyl	*N*,*N*-dimethylsulfonamido	52.0	155–156 (Benzene)
4-Chlorophenyl	*N*,*N*-diethylsulfonamido	71.0	131–132 (Ethanol)
4-Chlorophenyl		62.0	111—112 (Benzene)
2-Pyridyl		41.0	172–173 (dec) (Ethanol)

[a] Elemental analyses (C, H) for the new compounds reported here in agreement with theoretical values have been obtained and submitted for review. [b] After recrystallization.

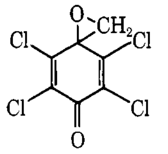
tion of nitrogen and the formation of 1,1-bis(trichloromethyl)ethylene oxide,



V

in good yield. The indicated structure was confirmed by characteristic epoxide near infrared absorption bands at 1.62 and 2.20 microns, with the second band about three times as intense as the first. The nuclear magnetic resonance spectrum showed only one sharp singlet at δ 3.62.

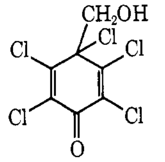
Similar results were obtained in the reaction of diazomethane and chloranil to form 2,3,5,6-tetrachloro-4-methyleneoxy-2,5-cyclohexadienone,



VI

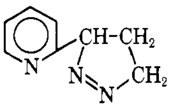
Again the epoxide structure was confirmed by the characteristic near-infrared absorptions at 1.63 and 2.21 microns. The infrared spectrum showed a strong absorption band at 1675 cm^{-1} for the conjugated carbonyl group. The nmr spectrum showed only one sharp singlet at δ 3.87.

Further confirmation of the indicated epoxide structure was given through reaction of VI with a solution of hydrogen chloride in dilute ethanol. An infrared spectrum of the product of this reaction showed OH absorption bands at 3550 and 3435 cm^{-1}, and conjugated carbonyl group absorption at 1675 cm^{-1}. The alcohol group was indicated to be primary rather than the isomeric tertiary alcohol by absorption bands at 1030 and 1272 cm^{-1}. Typical qualitative tests confirmed the presence of a primary alcohol group, and the structure of the product was believed to be



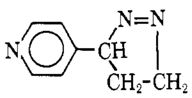
VII

Reaction of Diazomethane with Vinyl Pyridines. Both 2-vinyl and 4-vinyl pyridines reacted readily with diazomethane to give the corresponding pyrazolin-3-yl pyridines,



VIII

and



IX

The Δ^1-pyrazoline structure was indicated by lack of infrared absorption at 3335 cm^{-1} (NH) and by an absorption band at 1575 cm^{-1}, assigned to the N=N group. These compounds are readily air oxidized. The 2-(pyrazolin-3′-yl) pyridine was especially sensitive, turning yellow rapidly on exposure to air and then becoming progressively darker.

EXPERIMENTAL

Elemental analyses (C, H, N, Cl) (performed by Galbraith Laboratories, Knoxville, Tenn.) for the new compounds reported here in agreement with theoretical values have been obtained and submitted for review. Infrared spectra were obtained with a Beckman Model IR-5, and near infrared spectra were obtained with a Hitachi–Perkin-Elmer Model EPS-3T. Nuclear magnetic resonance spectra were obtained with a Varian Model HA-60 with TMS as internal standard and with deuteriochloroform as solvent.

Preparation of Schiff Bases. Solutions of equimolar amounts of the aldehyde and primary amine in either benzene or chloroform were heated at reflux with a water separator head until the theoretical amount of water had been collected. Removal of the solvent followed by several recrystallizations afforded the products.

Preparation and Use of Diazomethane. An ether solution of diazomethane, prepared by potassium hydroxide hydrolysis of *p*-toluenesulfonyl-methylnitrosamide (Diazald, Aldrich Chemical Co.) (*1*) was distilled directly into a stirred ether or aqueous dioxane solution of the other reactant (usually externally cooled). In general, 0.07 mole of this reactant was used, as well as sufficient Diazald and potassium hydroxide, to provide at least 0.1 mole of diazomethane, in accordance with the reference directions. After addition was complete, stirring was continued for an hour and the solution was then poured into precooled pressure bottles which were sealed and kept at room temperature for 1–3 days. Removal of ether was followed by direct vacuum distillation or recrystallization of the crude products.

Reactions of Diazomethane. *With Butadiene Sulfone (Preparation of III).* When the reaction described above was carried out with butadiene sulfone in ether solution for two days at room temperature, the yield after one crystallization was 36.4%; when done in 10% aqueous dioxane and ether for 40 hours at room temperature, the yield was 49% after one recrystallization. Three recrystallizations from 80% ethanol gave colorless crystals, mp 130–131°.

With Divinyl Sulfone (Preparation of IV). A rapid reaction took place with divinyl sulfone in ether with precipitation of colorless crystals. Filtration gave a quantitative yield of crude product, mp range 90–100°. Two recrystallizations from water gave colorless crystals, mp 103–105°, which slowly turned yellow on standing in air.

With Hexachloroacetone (Preparation of V). The reaction was run in ether and vigorous evolution of nitrogen occurred as the diazomethane was added. Removal of ether and distillation gave a 77% yield of colorless liquid, bp 72–73° (0.3 mm) n_D^{25} 1.5323.

With Chloranil (Preparation of VI). The reaction was run with 17.2 grams of chloranil as a partial solution in 200 ml of ether and vigorous evolution of nitrogen occurred throughout the addition of diazomethane. The reaction mixture was allowed to stand 3 days at room temperature and 4 grams of unreacted chloranil was removed by filtration. Removal of ether and one recrystallization of the crude solid product from 95% ethanol gave 10 grams (55%) of product. Two more recrystallizations from 95% ethanol gave light cream-colored crystals, mp 163–164°.

Compound (VI) (2.6 grams) was added to 2 ml of concentrated hydrochloric acid and then ethanol was added with stirring and warming until solution was effected. The solution was allowed to stand two days and water was then added to precipitate a solid product. The brown solid, after three recrystallizations from benzene and a small amount of ligroine, gave light cream-colored crystals (VII), mp 141–142°.

With 2-Vinylpyridine (Preparation of VIII). The diazomethane was added to a solution of 7.4 grams (0.07 mole) of 2-vinylpyridine in 35 ml of ether containing 1 ml of methanol at 0°. The solution was then kept in pressure bottles for two days at room temperature and removal of ether left 10 grams (95%) of crude product. This distilled at 97–98° (0.2 mm) and immediately formed colorless crystals which rapidly became colored on exposure to air.

With 4-Vinylpyridine (Preparation of IX). The reaction was run as for 2-vinylpyridine but without addition of methanol. After 2 days at room temperature a solid had precipitated. This proved very difficult to distill or to recrystallize. A pure product was obtained in 50% yield by washing the crude product with ether, mp 154–156°. The yield was improved to 80% in another experiment by concentration of the ether solutions to precipitate more crystals.

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Synthesis of Substituted Coumarins with Fluorescent Properties

LLOYD L. WOODS[1] and SAMIR M. SHAMMA
Texas Southern University, Houston, Tex. 77004

The synthesis of certain substituted coumarins (designated as ayapins) is described. The optical properties, including fluorescence, of the compounds are compared with two 7-dimethylaminocoumarins which were prepared by a novel procedure.

Ayapin (*3*) (6,7-methylenedioxycoumarin) homologs have been synthesized from sesamol, 3,4-methylenedioxyphenol, and β-ketonic esters in the presence of trifluoroacetic acid. The ayapins recorded in this report are 1 to 5 of the 1 to 7 series given in Table I. Compounds 1, 3, and 4 are strongly fluorescent.

EXPERIMENTAL

Preparation of Compounds 1 to 5. A mixture consisting of 0.05 mole of sesamol, 0.05 mole of the β-keto ester, and 30 ml of trifluoroacetic acid was refluxed for 3 hours, then poured into 400 ml of water. The solutions were chilled and filtered, and the precipitates dried in air to give the crude yield recorded in Table I.

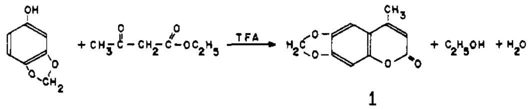
Table I. Coumarins[a]

No.[b]	β-Keto ester used	% Yield	Mp, °C
	Sesamol		
1	Ethylacetoacetate	98	183
2	Ethylbenzoylacetate	23	145–46
3	Ethyl 2-methyl acetoacetate	99	208–09
4	Ethyl 2-chloroacetoacetate	95	225
5	Ethyl 4-nitrobenzoylacetate	100	240–42
	4-Dimethylaminosalicylic Acid		
6	Ethylacetoacetate	55	144–45
7	Ethyl 4-nitrobenzoylacetate	88	226–27

[a] Elemental analyses for C, H (all compounds), N (last three compounds), and Cl (fourth compound) were submitted for review and are in agreement with theoretical values. [b] 4-Methyl-6,7-methylenedioxycoumarin. 6,7-Methylenedioxy-4-phenylcoumarin. 3,4-Dimethyl-6,7-methylenedioxycoumarin. 3-Chloro-4-methyl-6,7-methylenedioxycoumarin. 6,7-Methylenedioxy-4-(4-nitrophenyl)coumarin. 7-Dimethylamino-4-methylcoumarin. 7-Dimethylamino-4-(nitrophenyl)coumarin.

Compound 2 was recrystallized from ethanol and water. The analytical samples were obtained by recrystallization from ethyl acetate and heptane. All of the substances of this series were dried several days in a vacuum desiccator.

An nmr spectrum of the model compound 1 gave methyl protons at 2.37 ppm and methylene protons at 6.04 ppm; protons at positions 3, 8, and 5 were 6.13, 6.79, and 6.92 ppm, respectively, in chloroform solvent. The spectrum confirms the postulated structure of the substance indicated in Scheme I.



1

The bis-4-nitrophenacyl derivative of 1 (1a) was prepared in the usual fashion and recrystallized from absolute ethanol, (mp 95° C).

Table II. Infrared Absorption Maxima in the Range of 1750 to 1550 cm^{-1} and Ultraviolet Absorption Maxima in Mμ (log ε)[b]

No.	Ir absorption	Uv absorption
1	1693, 1624W, 1581	208(4.34), 235(4.30), 290(3.84), 345(4.15), 356(4.10)
2	1703, 1633, 1560	210(4.71), 241(4.50), 298(4.06), 352(4.34), 356(4.35), 365(4.29)
3	1689, 1635W, 1580	208(4.32), 235(4.24), 290(3.72), 341(4.19), 355(4.08)
4	1712, 1620, 1560	210(4.50), 238(4.30), 287(3.85), 352(4.30), 355(4.30), 364(4.24)
5	1722, 1628, 1561	210(4.55), 235(4.31), 274(4.28), 354(4.12)
6	1708, 1600	212(4.60), 242(4.31), 369(4.43)
7	1720, 1623	214(4.65), 254(4.39), 296(3.99)

[a] Spectra run on Beckman-IR-8 with KBr pellets, W = weak. [b] Spectra run on Bausch and Lomb Spectronic-505 in spectrograde methanol.

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[1] To whom correspondence should be addressed.