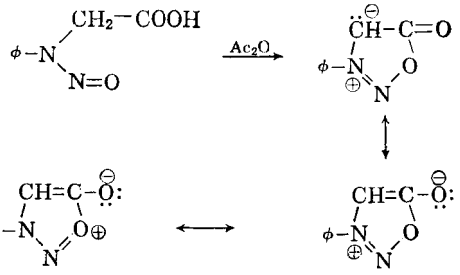
Synthesis of Sydnones as Potential Therapeutic Agents

By LEMONT B. KIER and DEVINDRA DHAWAN

A number of new 3-alkyl sydnones have been prepared as potential therapeutic agents. A preliminary pharmacological evaluation indicated that these compounds were central nervous system stimulants. The partition coefficients between chloroform and water were determined and a correlation was found between this and the millimole dosage per kilogram in the sydnones with nonfunctional side chains. Ultraviolet and infrared data are reported for the sydnones.

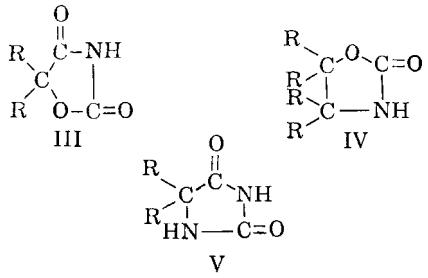
THE FIRST mesoionic compounds known as sydnones (I) were synthesized in 1935 by Earl and Mackney at the University of Sydney (1). They observed that when N-nitroso-N-phenyl glycine is heated with acetic anhydride, water is lost and a compound having a 1,2,3-oxadiazole ring structure is formed:



The bicyclic structure (II), originally postulated, was unacceptable to subsequent investigators (2–4) who showed that the sydnones are resonance hybrids of numerous canonical forms, including the three above. Dipole moment (5, 6), X-ray analysis (7), and molecular-orbital treatment (8) have subsequently substantiated this structural assignment. The term "mesoionic" has been coined for this type of system and has been defined (9) as a five- or six-membered heterocyclic compound, which cannot be represented satisfactorily by any one canonical structure. It possesses a sextet of π electrons in association with all of the ring atoms. Further, the ring bears a fractional positive charge balanced by a corresponding negative charge on a covalently attached exocyclic atom or group. Structures like I are used by convention for mesoionic compounds.

A review of the literature revealed no pharma-

I II

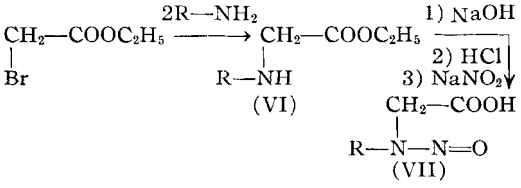


III IV V

cological study of these compounds as possible chemotherapeutic agents.[1] A comparison of the sydnone (I) structure with that of the 2,4-oxazolidinediones (III), 2-oxazolidinone (IV), and hydantoins (V) revealed some similarity. These last three are known anticonvulsants though alkylation of the nitrogen atom will frequently reverse the action, producing a convulsant (10, 11).

With these thoughts in mind, a systematic study of some sydnones and other mesoionic compounds was initiated in this laboratory. For this initial study a number of new 3-substituted sydnones were prepared representing the simplest type of substitution on the ring.

Among several routes leading to the nitrosoamino acid (VII), the following one was chosen



A recent study on the synthesis of α-alkylamino esters (12) of the type VI showed that a higher yield could be obtained by using an α-bromo-ester and two equivalents of the amine. The second equivalent of the amine proved to be an acid scavenger superior to trialkyl amines or inorganic bases. All of the α-alkylamino esters in our study were high-boiling liquids which could be easily purified by vacuum distillation. See

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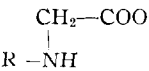
[1] Since completion of this manuscript, another report covering antitumor activity of several sydnones has been published (23).

Table I. Hydrolysis of VI was done in refluxing base. Isolation and purification of the resulting α-alkylamino acids proved to be very tedious and costly. Since the α-alkylamino esters could be easily purified and characterized, isolation of their hydrolysis products was considered unnecessary. This product was then nitrosated *in situ* after rendering the solution strongly acid. All of the nitrosoamino acids (VII) were solids and were purified with no difficulty. See Table II.

A number of reagents have been employed for the ring closure of VII to the sydnone including acetic anhydride and trifluoroacetic anhydride (4, 13). The mechanism involves the formation of a mixed anhydride with the nitroso acid (VII). Because of the grater lability of the C_4 hydrogen, due to the absence of an alkyl group on the same carbon, it was felt that acetic anhydride would be a satisfactory ring-closing reagent. The exclusion of water in this step was essential for maximum yield, hence freshly distilled acetic anhydride was employed throughout. The initial heating followed by a prolonged period of standing in the dark was found to give the best yield of sydnone (I). The solids were generally crystallized from water while the liquids were vacuum distilled. Several explosions resulted from distilling the allyl sydnone until it was distilled under nitrogen. See Table III for analyses.

TABLE I.—ETHYL ALKYLAMINO ACETATES



R	Formula	% Yield	B.p., °C./ mm.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Isopropyl	$C_7H_{15}O_2N$	53	36/10	57.90	10.41	9.65	57.53	10.13	9.36
Propyl	$C_7H_{15}O_2N$	72	40/0.25	57.90	10.41	9.65	57.73	10.44	9.69
Allyl	$C_7H_{13}O_2N$	57	67/20	58.72	9.15	9.73	58.54	8.90	9.87
sec-Butyl	$C_8H_{17}O_2N$	34	57/0.4	60.34	10.76	8.80	60.30	10.84	8.90
tert-Butyl	$C_8H_{17}O_2N$	38	65/3	60.34	10.76	8.80	60.13	10.73	8.63
Furfuryl	$C_9H_{13}O_3N$	36	90/0.1	59.00	7.15	7.65	59.36	7.29	7.33
Phenethyl	$C_{11}H_{15}O_2N$	72	70/0.5	68.37	7.82	7.25	68.62	8.20	6.88
tert-Octyl[a]	$C_{12}H_{25}O_2N$	55	75/22	66.93	11.70	6.51	66.59	11.89	6.53

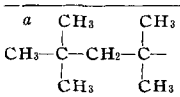
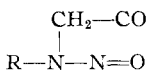
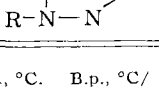
[a] 

TABLE II.—N-NITROSO ALKYLAMINO ACETIC ACIDS



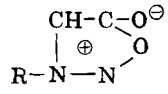
R	Formula	% Yield	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Isopropyl	$C_5H_{10}O_3N_2$	50	129–130	41.09	6.80	19.17	41.25	6.90	18.90
Propyl	$C_5H_{10}O_3N_2$	51	72–74	41.09	6.80	19.17	40.90	6.69	18.96
Allyl	$C_5H_8O_3N_2$	65	20	41.66	5.59	19.44	41.35	5.74	19.75
sec-Butyl	$C_6H_{12}O_3N_2$	65	79–81	44.99	7.55	17.49	44.87	7.26	17.26
tert-Butyl	$C_6H_{12}O_3N_2$	56	109–110	44.99	7.55	17.49	54.29	7.19	17.78
Furfuryl	$C_7H_8O_4N_2$	50	114–115	45.65	4.38	15.21	45.47	4.39	14.91
Phenethyl	$C_{10}H_{12}O_3N_2$	55	134–136	57.68	5.81	13.46	57.50	5.90	13.21
tert-Octyl	$C_{10}H_{20}O_3N_2$	85	135–137	55.53	9.32	12.95	55.22	9.12	12.74

TABLE III.—N-ALKYL SYDNONES



R	Formula	% Yield	M.p., °C.	B.p., °C/ mm.	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
Isopropyl	$C_5H_8N_2O_2$	63	54–55.5	...	46.87	6.29	21.89	47.06	6.38	21.92
Propyl	$C_5H_8N_2O_2$	68	...	94/2.5	46.87	6.29	21.89	46.68	6.36	21.79
Allyl	$C_5H_6N_2O_2$	71	...	70/2	47.62	4.80	22.22	47.78	5.17	22.58
sec-Butyl	$C_6H_{10}N_2O_2$	67	...	160/3	50.70	7.09	19.71	50.85	6.95	19.99
tert-Butyl	$C_6H_{10}N_2O_2$	55	168–170	...	50.70	7.09	19.71	50.53	7.19	19.87
Furfuryl	$C_7H_6N_2O_3$	60	94–95	...	50.60	3.64	16.86	50.48	3.66	16.53
Phenethyl	$C_{10}H_{10}N_2O_2$	52	...	111/5	63.14	5.30	14.73	63.37	5.32	14.53
tert-Octyl	$C_{10}H_{18}N_2O_2$	72	93–95	...	60.58	9.15	14.14	60.39	9.31	14.36

TABLE IV.—SYDNONE PHYSICAL AND PHARMACOLOGICAL DATA



R	Ethyl Alcohol λ max. mμ	ε	C-O, λ Nujol μ	Pc $\frac{C_1HCl_3}{H_2O}$	CD_{50}, mmole/Kg.	LD_{50}, mmole/Kg.
Allyl	290	6000	5.75	0.90	1.11	1.21
Isopropyl	289	6600	5.75	1.3	2.96	3.75
Propyl	288	6600	5.75	1.5	1.60	1.87
Furfuryl	290	6500	5.85	3.4	>2.5	>2.5
tert-Butyl	290	5900	5.80	4.6	0.87	1.30
sec-Butyl	290	6300	5.75	6.4	1.13	1.55
tert-Octyl	292	6100	5.81	9.6	0.25	0.31
Phenethyl	286	5800	5.75	20.	...	>6.0

The ultraviolet absorption maxima fell in the range reported for a few of these compounds (14–16). An infrared maximum at 5.75–5.85 μ was found for each sydnone, which can be ascribed to the pseudo-keto group (17–19). In addition, each sydnone had a strong absorption band at 9.5 μ which is in the region of the C—O stretching frequencies (20).

A preliminary pharmacological evaluation (21) indicated that all but the phenethyl sydnone were central nervous system stimulants with a particularly stimulating effect on respiration. As comparative parameters the LD_{50} and CD_{50} (convulsive dose) i.p. in mice were chosen. See Table IV.

In an attempt to relate structural effect with pharmacological action, the partition coefficients between chloroform and water were determined. Because of the simple nature of the modifying groups it was felt that the ring itself imparted the pharmacological action while the side chain determined the rate of absorption and transport to the receptor site.

If the pharmacological action was chiefly central, as preliminary data indicated, then the sydnones with a greater affinity for lipid solvents would be expected to penetrate the lipid barrier into the CNS with greater facility. This conjecture was proven to be correct as far as the sydnones with nonfunctional aliphatic side chains. Those with a higher partition coefficient between chloroform and water were more active in eliciting convulsions on a millimole per kilogram basis. Those with functional groups in the side chain such as the allyl, phenethyl, and furfuryl sydnones did not follow this pattern. Both of these aspects of mono and disubstituted sydnones are under current study in this laboratory.

EXPERIMENTAL [2]

Alkylamino Esters (VI).—A solution of two moles of the amine in 500 ml. of anhydrous ether was cooled to 0° in a two-necked flask equipped for stirring. To this was added dropwise, one mole of ethyl bromoacetate in 150 ml. of anhydrous ether. The temperature was maintained at 0°. The mixture was stirred for 3 hours then allowed to stand overnight. The precipitate was filtered off and the filtrate vacuum distilled. In all cases the products were liquids. See Table I for yield, b.p., and analyses. Infrared analyses corroborated the assigned structures.

Hydrolysis of Esters.—The alkylamino esters (VI) were hydrolyzed by refluxing them with 1.5 equivalents of aqueous sodium hydroxide. The refluxing was stopped when the reaction mixture formed a single phase. The solution was then cooled and made acid to pH 2 with hydrochloric acid.

Nitrosoamino Acids (VII).—The strongly acidified solution of the alkylamino acid was cooled to 0° in an ice-salt bath and then treated dropwise with a solution containing 1.1 equivalents of sodium nitrite. This reaction mixture was stirred for two hours at 0° after the addition. The crude nitrosoamino acid was filtered and recrystallized from ether, acetone, or mixtures of the two. All of the nitrosoamino acids gave positive Liebermann tests (22). See Table II for yields, m.p., and analyses.

3-Alkyl Sydnones (I).—The nitrosoamino acids (VII) were added to a five molar excess of freshly distilled acetic anhydride and warmed on a steam bath for 3 hours. The reaction mixture was allowed to stand for three days at room temperature in the dark. The acetic anhydride was removed under vacuum using toluene to remove the last traces. The sydnone was then either distilled under vacuum or crystallized from ether. Distillation of the 3-allyl sydnone had to be done under nitrogen in order to prevent the ignition or explosion of the product. See Table III for m.p. or b.p., yield, and analyses. The infrared and ultraviolet spectra were obtained for each compound. See Table IV.

Partition Coefficients.—The partition coefficients of the sydnones (I) were obtained between water-saturated chloroform and chloroform-saturated water. Several concentrations of each compound in water-saturated chloroform at 23° were shaken for 1 hour with varying quantities of chloroform-saturated water. The concentration in the chloroform before and after shaking with the water was determined from the ultraviolet absorption at the maximum. An average of at least four determinations for each sydnone was used. See Table IV.

[2] All melting points were done on the Kofler apparatus and are corrected. Analyses were performed by Weiler and Strauss Microanalytical Labs., Oxford, England and Galbraith Laboratories, Knoxville, Tenn.

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Protective Coatings XIII. Amphoteric Polyvinylpyridine Derivatives

By TADAO IDA, SHUZO KISHI, SHOJI TAKAHASHI, and ISAMU UTSUMI

Polyampholites of vinylpyridine or its alkyl derivatives with acrylic or methacrylic acid and the copolymers of these compounds with other vinyl derivatives were synthesized and studied as protective coating agents for tablets. Results showed that the synthesized copolymers had adequate viscoelasticity, protective qualities, and disintegration characteristics to serve as protective coating agents.

POLYAMPHOLYTES of vinylpyridine or its derivatives with acrylic or methacrylic acid and copolymers of those with other vinyl compounds were experimentally synthesized. The purpose of synthesis was to obtain such protective-coating agents as to exhibit protective activity on drugs and solubility in both gastric and intestinal juice. Solubility, water vapor permeability through the film, and viscoelasticity were tested on each of copolymers.

The practical coatings on tablets were also carried out and disintegration time of the coated tablets, absorption of moisture and aging deterioration of the active ingredients were subsequently investigated. Most of the compounds have shown outstanding properties as protective-coating agents.

In the preceding reports, observations were made on the applicability of polyvinylpyridine derivatives and other compounds to protective-coating agents (1). All preparations coated with these compounds were easily dissolved in acid of gastric juice to release medicament. However, it is believed that there are marked differences in gastric acid secretion among individuals, particularly those patients with hypoacidity or anacidity. In this sense, it is feared that preparations coated with one of these compounds may be not disintegrated by gastric juice. In order to overcome this disadvantageous property of these compounds, preparations should be coated with such protective-coating agents as to be insoluble near the neutral pH but disintegrate favorably both in gastric juice of lower acidity and in intestinal juice.

Attempts to elucidate the properties of the polyampholytes obtained by the reaction of vinylpyridine or its alkyl derivatives with methacrylic or acrylic acid were made to examine their eligibilities for protective-coating agents.

Copolymerization of 2-vinylpyridine and methacrylic acid and physico chemical properties of the products have been reported by Alfrey (2) and Katchalsky (3), respectively. There have been other reports on the copolymerization of the main body of acrylonitrile with vinylpyridine, methacrylic acid or other vinyl compounds for textile-improving (4–6). On the other hand, no reported study has dealt with these products as coating agents for medicaments.

As starting monomers 4-vinylpyridine (4VP), 2-vinylpyridine (2VP), 2-methyl-5-vinylpyridine (MVP), and 2-vinyl-5-ethylpyridine (VEP) were used for basic components, whereas methacrylic acid (MAA) and acrylic acid (AA) were used for acidic components. Styrene (St), methylacrylate (MA), and acrylonitrile (AN) were used as other monomers.

Copolymers were synthesized from any two or three components using either a catalyst of benzoylperoxide (BPO) or α,α'-azo-bis-isobutyr-

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