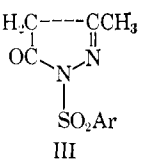
TABLE II

$CH_3CCH_2CO_2C_2H_5$
$\|$
$NNHSO_2Ar$
II

Ar	Mp, °C[a]	Yield, %[b]	Method	Formula[c]	Analyses
p-$CH_3OC_6H_4$	110–111	65.8	C	$C_{13}H_{18}N_2O_5S$	C, H, N
p-$C_2H_5OC_6H_4$	106–107	55.8	C	$C_{14}H_{20}N_2O_5S$	C, H, N
$C_6H_5CH_2$	79–80	52.7	D	$C_{13}H_{18}N_2O_4S$	N

[a–c] See footnotes *a–c* in Table I.

TABLE III



III

Ar	Mp, °C dec[a]	Yield, %[b]	Formula[c]	Analyses
p-$CH_3OC_6H_4$	137–138	34.5	$C_{11}H_{12}N_2O_4S$	C, H, N
p-$C_2H_5OC_6H_4$	168	44.6	$C_{12}H_{14}N_2O_4S$	C, H
$C_6H_5CH_2$	120–122	40.1	$C_{11}H_{12}N_2O_3S$	C, H, N

[a–c] See footnotes *a–c* in Table I.

50 ml of 95% EtOH, 0.004 mole of acetylacetone was added. The solution was refluxed 1–2 hr, then left overnight at 3°. Recrystallization from MeOH gave white crystals.

Method B.—Equimolar quantities of acetylacetone and the 1-arylsulfonylhydrazide (0.002 mole), were dissolved in 30 ml of DMF at 0°, and 3 drops of 2 *N* HCl were added. The solution was stirred at room temperature for 2 hr, then left at 3° overnight. The transparent white crystals thus obtained were recrystallized from 1:1 Et_2O–petroleum ether (40–60°).

1-Arylsulfonylhydrazones of Ethyl Acetoacetate (II) (Table II). Method C.—To a solution of 0.002 mole of the 1-arylsulfonylhydrazide in 50 ml of 95% EtOH, was added 0.004 mole of ethyl acetoacetate. The solution was refluxed 1–2 hr, then left overnight at 3°. The white crystals were filtered and recrystallized from EtOH.

Method D.—Equimolar quantities (0.002 mole) of ethyl acetoacetate and the 1-arylsulfonylhydrazide were dissolved in 50 ml of 95% EtOH, and 2 ml of 5% AcOH was added. The solution was stirred at room temperature for 2 hr, then left overnight at 3°. The white crystals were filtered and recrystallized from 1:1 MeOH–H_2O.

3-Methyl-N¹-arylsulfonyl-5-pyrazolones (III) (Table III).—The 1-arylsulfonylhydrazone of ethyl acetoacetate (0.002 mole) was dissolved in 10 ml of 5% Na_2CO_3 and held at 80–90° for 2–3 hr. It was then cooled and brought to pH 3 with 0.6 *N* HCl, then left overnight at 3°. The white powder obtained was recrystallized from H_2O.

Acknowledgment.—We thank Dr. Juan Estaven of the University of Barcelona for the elemental analyses and also the Diamond Shamrock Corp. for generous supplies of several reagents.

Preparation of (Carboxymethyl)cyclohexyldimethylammonium Chloride Hydrazide

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In studies of the reaction of cationic hydrazides with carbonyl groups in periodate-oxidized starches[1,2] we synthesized (carboxymethyl)cyclohexyldimethylammonium chloride hydrazide by the method of Girard and Sandulesco[3] for Girard T reagent. The new compound might be of value in isolating ketones from steroid mixtures[3] and aldehydes from autoxidized fats and oils.[4]

Experimental Section

(Carboxymethyl)cyclohexyldimethylammonium Chloride Hydrazide.—N,N-Dimethylcyclohexylamine[5] (53.4 g, 0.42 mole) was added dropwise to a stirred solution of ethyl chloroacetate (49.0 g, 0.40 mole) in 100 ml of absolute EtOH at 5°. The mixture was stirred at 5–10° for 30 min, then heated at 60–70° for 1 hr, and allowed to stand at room temperature overnight to form the intermediate ethyl ester of (carboxymethyl)cyclohexyldimethylammonium chloride in solution.

Hydrazine of 95+% purity (13.5 g, 0.40 mole) was added dropwise to this solution during 15 min of continuous stirring with the temperature rising to 50–60°. The reaction mixture was maintained at this temperature range for 1 hr and then concentrated *in vacuo* to about 100 ml. When an equal volume of EtOAc was added to the concentrate and it was kept at 2° for 36 hr, crystallization occurred. The extremely hygroscopic product was filtered off in an atmosphere of 11% relative humidity and dried *in vacuo* over P_2O_5. Recrystallization from EtOAc–EtOH (5:1) gave 57.6 g (61%) of the hydrazide, mp 160–164°. *Anal.* ($C_{10}H_{22}ClN_3O$) C, H, N, Cl.

Acknowledgments.—We thank Mrs. Clara McGrew and Mrs. Bonita Heaton for the microanalyses.

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3,3-Disubstituted Ethyl Carbazates[1]

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The antitumor activity of such hydrazine derivatives as MIH [$CH_3NHNHCH_2C_6H_4CONHCH(CH_3)_2$], 1-acetyl-2-picolinoylhydrazide, and 5-(3,3-dimethyl-1-triazeno)-4-imidazolecarboxamide, has encouraged us to prepare some 3,3-disubstituted ethyl carbazates for screening.

The lack of significant activity (Table I) in those compounds (**1–4**) which are not alkylating agents would seem to indicate that the activity of **5** is related to its alkylating properties rather than to any properties it may have as a substituted hydrazine.

Experimental Section[2]

Ethyl 3,3-Bis(chloroallyl)carbazates.—Compounds **1–4** were prepared from the appropriate dichloroalkene (0.5 mole), ethyl carbazate[3] (0.25 mole), and NaOH (0.5 mole) in absolute EtOH (50 ml). The mixture was shaken with cooling for 1 hr, followed by shaking for an additional 8 hr, then filtered. The filtrate was

(1) This work was supported by Research Grant CA-06586 from the National Cancer Institute, National Institutes of Health, to the University of Kentucky Research Foundation.

(2) Melting points were taken on a Fisher-Johns melting point block and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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(1) C. L. Mehltretter, T. E. Yeates, G. E. Hamerstrand, B. T. Hofreiter, and C. E. Rist, *Tappi*, **45**, 750 (1962).
(2) T. E. Yeates and C. L. Mehltretter, *ibid.*, **48**, 655 (1965).

TABLE I
R_2NNHCO_2Et

No.	R	Mp, °C	Yield, %	Formula	Analyses	T. C.,[a] %	Dose, mg/kg
1	$CH_2{=}CClCH_2$	56–57	12	$C_9H_4Cl_2N_2O_2$	C, H	85	50
2	$CH_2{=}CBrCH_2$	64–69	7	$C_9H_{14}Br_2N_2O_2$	C, H	84	25
3	*cis*-$ClCH{=}CHCH_2$	81–82	17	$C_9H_{14}Cl_2N_2O_2$	N	101	50
4	$CH_3CCl{=}CHCH_2$	87–88	17	$C_{11}H_{18}Cl_2N_2O_2$	C, H	109	25
5	$TsOCH_2CH_2$	98–99	8	$C_{21}H_{28}N_2O_8S_2$	C, H	13	400
						30	200
						66	100
						67	50

[a] Activity against Walker Carcinosarcoma 256 subcutaneous (**1**–**4**) or intramuscular (**5**). The evaluations were done through the facilities of the Cancer Chemotherapy National Service Center.

evaporated under reduced pressure, the residue was extracted with Skellysolve A, and the extract was cooled to give product which could be recrystallized from Skellysolve A.

Ethyl 3,3-Bis(2-tosyloxyethyl)carbazate.—To a stirred solution of ethyl carbazate (66 g, 0.63 mole) in 200 ml of 50% HOAc at 0° was added ethylene oxide (74 g, 1.68 moles). The solution was stirred at 0–5° for 3 hr, then allowed to warm to room temperature. After 2 days, it was evaporated under reduced pressure (steam bath). The crude $(HOCH_2CH_2)_2NNHCO_2Et$ thus obtained was used directly. Thus, 5 g (0.026 mole) of $(HOCH_2CH_2)_2NNHCO_2C_2H_5$ and *p*-TsCl (11.4 g, 0.06 mole) was stirred for 2 hr with 100 ml of a 20% NaOH solution and filtered, and the precipitate was washed (H_2O) and recrystallized (*i*-PrOH, MeOH–H_2O) to give 1.3 g (7.8%), mp 98–99°.

Book Reviews

Synthetic Procedures in Nucleic Acid Chemistry. Volume 1. Preparation of Purines, Pyrimidines, Nucleosides, and Nucleotides. Edited by W. WERNER ZORBACH and R. STUART TIPSON. Interscience Division, John Wiley and Sons, New York, N. Y. 1969. vi + 570 pp. 16 × 23.5 cm. $16.95.

This book contains 163 experimental directions for the synthesis of compounds announced in its title. The material is arranged similar to that found in "Organic Syntheses." Structural formula schemes permit a quick survey of the steps involved, and a short introduction states the significance and synthetic procedure. This is followed by cookbook directions for one or several similar compounds, and by references. The volume should be useful for all those working in this field.

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Advances in Chemotherapy. Volume 3. Edited by ABRAHAM GOLDIN, F. HAWKING, and R. J. SCHNITZER. Academic Press Inc., New York, N. Y. 1968. xi + 407 pp. 23.5 × 15.5 cm. $18.50.

Volume 3 of "Advances in Chemotherapy" is a blend of the present and the future in chemotherapy. Three chapters deal with "classical" structure–activity screening and evaluation studies in selected parasitic diseases. Two chapters present subjects presently peripheral to the general field of chemotherapy, but of definite interest in the near future. The sixth chapter is a succinct review of statistical procedures useful in experimental chemotherapy.

Any new review of the chemotherapy of parasitic diseases will perforce be compared to the corresponding portion of R. J. Schnitzer and F. Hawking's monumental "Experimental Chemotherapy." The chapters on the chemotherapy of cestode infections by J. E. D. Keeling and the chemotherapy of trematode infections by G. Lämmler cover the literature subsequent to "Experimental Chemotherapy," and are written in a similar format. The chapter on the chemotherapy of trichomoniasis by R. M. Michaels contains a useful section on the biology and biochemistry of the parasite. However, the extensive citations to structure–activity studies based on *in vitro* testing, where little or no correlation to *in vivo* activity is evident, detracted from this reader's impression of the chapter. All three chapters will be of value to medicinal chemists engaged in parasitic chemotherapy, as a convenient up-dating of "Experimental Chemotherapy."

The most interesting chapter in this volume is that by A. Allison on the role of lysosomes in the action of drugs and hormones. Anyone concerned with the mode of action of chemotherapeutic agents will find it stimulating and thought provoking.

The chapter on the antimitotic activity of polyanions by W. Regelson will be difficult reading for those involved in chemotherapy studies on agents with discrete molecular structures. However, this review of the diverse biological activities of natural and synthetic polyanions will be a useful springboard for the interpretation of future developments, particularly in virus research.

The chapter on selected statistical methods by J. A. Waitz and A. J. Dresner will be chiefly of interest to biologists and parasitologists concerned with the vagaries of experimental parasitic infections.

The over-all impression of this volume is quite favorable, and only a few inconsequential errors of a chemical nature were noted. Medicinal chemists, in particular, should carefully read the closing remarks by Dr. Keeling (pp 143–148) and Professor Lämmler (pp 238–239).

ORGANIC CHEMICAL RESEARCH SECTION
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Physiological Chemistry of Lipids in Mammals. By EDWARD J. MASORO. W. B. Saunders Co., Philadelphia, Pa. 1968. xi + 304 pp. 16 × 23.5 cm. $7.75.

In a foreword to this volume, the author states that it is the first of a series under his general editorship. Succeeding volumes are to cover, in sequence, Physiological Chemistry of Proteins and Nucleic Acids in Mammals, Physiological Chemistry of Carbohydrates in Mammals, Energy Metabolism of Mammals, and Acid–Base Homeostasis: Its Physiology and Pathophysiology. His thesis that a gap has developed between modern biochemistry and mammalian physiology and pathology due to the former's evolution *via* research with cell-free systems or simple