most active compound. As is evident from Table III, all pyrazolines exhibiting a greater degree of protection elicited a lower pentylenetetrazol-induced mortality during 24 hr in the experimental animals.

These studies, exhibiting pronounced anticonvulsant activity of substituted pyrazolines, were unable to provide a correlation between their anticonvulsant activity and their ability to inhibit monoamine oxidase activity as a biochemical basis of their anticonvulsant activity. Further studies dealing with the synthesis of other related structures carrying different substituents and the determination of their ability to inhibit purified enzyme preparations may possibly reflect the biochemical basis of the anticonvulsant activity of substituted pyrazolines.

REFERENCES

(1) L. G. Polevoi, *Tr. Nauch. Konf. Aspir. Ordin., 1-yi (Pervyi) Mosk. Med. Inst., Moscow,* **1964,** 159; through *Chem. Abstr.,* **65,** 19147d(1966).

(2) V. M. Avakumov and Y. M. Batulin, *Farmacol. Toksikol.,* **31,** 402(1968); through *Chem. Abstr.,* **69,** 75439h(1968).

(3) L. G. Polevoi, A. N. Kudrin, I. I. Grandberg, and A. N. Kost, *Izv. Timiryazev. Sel'skokhoz. Akad.,* **1,** 192(1968); through *Chem. Abstr.,* **69,** 1557y(1968).

(4) Y. M. Batulin, *Farmakol. Toksikol.,* **31,** 533(1968); through *Chem. Abstr.,* **70,** 2236a(1969).

(5) M. C. Hart and E. H. Woodruff, *J. Amer. Chem. Soc.,* **58,** 1957(1936).

(6) M. Krajl, *Biochem. Pharmacol.,* **14,** 1684(1965).

(7) S. S. Parmar, C. Dwivedi, B. Ali, and R. S. Misra, *J. Med. Chem.,* **15,** 846(1972).

ACKNOWLEDGMENTS AND ADDRESSES

Received December 17, 1973, from the *Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow, India, and the ‡Department of Pharmacology, School of Medicine, Vanderbilt University, Nashville, TN 37203

Accepted for publication March 29, 1974.

Supported by U.S. Public Health Service, National Institutes of Health Grants ES 00782, ES 00267, and DA 00141, and by the Council of Scientific and Industrial Research, New Delhi, India.

The authors thank Professor K. P. Bhargava and Professor Stanley J. Brumleve for their advice and encouragement. Grateful acknowledgment is made to Dr. M. L. Dhar and Dr. Nitya Anand of the Central Drug Research Institute, Lucknow, India, for providing microanalysis facilities, and to the Council of Scientific and Industrial Research, New Delhi, India, for providing a Junior Research Fellowship to B. Pandey.

ˣ To whom inquiries should be directed. Present address: Department of Physiology and Pharmacology, School of Medicine, University of North Dakota, Grand Forks, ND 58201

Novel Synthesis of Bifunctional Acid-Esters

SUDHAKAR KASINA, KIM WAH NG, and JAY NEMATOLLAHIˣ

Abstract □ A novel method was developed for the synthesis of acid-esters *via* monodemethylation of a dimethyl ester by 1,1-dimethylhydrazine and subsequent conversion of the resulting trimethylhydrazonium ester to the desired acid-ester. The method is facile and seems to have a wide range of applicability.

Keyphrases □ Acid-esters, bifunctional—novel synthesis using 1,1-dimethylhydrazine and a dimethyl ester and conversion of the resulting trimethylhydrazonium ester □ Trimethylhydrazonium ester—intermediate in synthesis of bifunctional acid-esters □ 1,1-Dimethylhydrazine—utilized in novel synthesis of bifunctional acid-esters

Quite often the synthesis of compounds containing both an acid and an ester moiety (acid-ester) requires tedious experimental design and manipulation. This is particularly true with cyclic systems from which no anhydride (a widely used precursor for the acid-ester) can be synthesized, due either to nonproximity of the functional groups or to development of severe strain if the anhydride is formed.

This paper describes a novel and efficient solution to the problem of preparing bifunctional compounds containing both a carboxy and a carbomethoxy functional group.

DISCUSSION

The developed method utilizes 1,1-dimethylhydrazine to effect the monodemethylation of an aliphatic or aromatic dimethyl ester and subsequent conversion of the resulting trimethylhydrazonium ester to the desired acid-ester (Scheme I). Either the addition of dilute hydrochloric acid to the trimethylhydrazonium salt followed by ether extraction or the use of silica gel column chromatography provided the free acid-ester. The latter method, although laborious, is an attractive feature, particularly for compounds containing acid-sensitive moieties or whose acid-esters exist in zwitterion forms and are, therefore, highly water soluble and ether insoluble.

That this method of synthesis of acid-esters is facile and has broad application in both aliphatic and aromatic systems is shown by the examples in Table I. A possible exception seems to be five-membered heterocyclic rings with vicinal methyl ester substituents. Under the generally applied reaction conditions, no bifunctional acid-ester compounds were afforded from the dimethyl esters of either 4,5-imidazoledicarboxylic acid or 3,4-pyrazoledicarboxylic acid[1]. However, more five-membered rings with vicinal diesters must be investigated before generalizations can be made concerning their reactions with 1,1-dimethylhydrazine.

The reaction of dimethyl 3,5-pyridinedicarboxylate with 1,1-dimethylhydrazine (Scheme I) exemplifies the general procedure. The structural formulas of all synthesized compounds as well as their melting points, spectral data, and elemental analyses are shown in Table I.

The molecular structures of the reaction intermediates, the bifunctional trimethylhydrazonium esters, and the final products, the acid-esters, were elucidated by using IR, NMR, and mass spectrometry. Elemental analyses were carried out for only a few crystalline hydrazonium salts[2], in an effort to establish an unequivocal correlation between molecular structures and spectral

[1] The reaction product is somewhat complex and is currently being investigated.

[2] Some hydrazonium salts were observed to be semisolid and extremely hygroscopic, and no elemental analyses were attempted for them. Spectral data of the given trimethylhydrazonium and its corresponding acid-ester were used for determining molecular structure.

Table I—Data for Trimethylhydrazonium Esters and Acid-Esters

Compound	Yield, %	Analysis, %[a] Calc.	Analysis, %[a] Found	Mass Spectroscopy Results	IR Bands, cm^{-1}	NMR Peaks[b,c], δ	Melting Point	Reference
I		C 56.69 H 7.08 N 11.02	56.46 7.34 11.22	163[d]	3220(NH); 1730, 1580(C=O)[e]	3.45(s, NCH_3); 4.00(s, OCH_3); 7.52–7.85(m, C_6H_5)	144°	1
II	90			180	1730, 1698(C=O)	4.00(s, OCH_3); 7.52–8.15 (m, C_6H_5)	75–78° (lit. 84°)	2
III	43			180[f]	3210(NH); 1725, 1625, 1580(C=O)	3.53(s, NCH_3); 4.15(s, OCH_3); 7.58–8.90(m, C_6H_5)	134–138°	
IV	90			180	1730, 1680(C=O)	4.05(s, OCH_3)	189–192° (lit. 193°)	3
V	51	C 56.69 H 7.08 N 11.02	56.43 6.99 11.05	180[f]	3210(NH); 1730, 1592, 1550 (C=O)	3.50(s, NCH_3); 4.12(s, OCH_3); 8.33(s, C_6H_5)	176–178°	
VI	90			180	1728, 1690(C=O)	4.12(s, OCH_3); 8.27(s, C_6H_5)	228–229° (lit. 230°)	4
Mixture of VII and VIII	23			164[d]	1740, 1605(C=O)	3.47(s, NCH_3); 4.18 and 4.20(s, OCH_3); 8.40–9.27(m, pyridine)		
IX					1735, 1705(C=O)	4.20(s, OCH_3); 8.35–9.10(m, pyridine)	105°	5
X					1735, 1695(C=O)	4.17(s, OCH_3); 8.33–9.18(m, pyridine)	123°	5
XI	61			181[f]	3400(NH); 1725, 1610(C=O)	3.45(s, NCH_3); 4.20(s, OCH_3); 9.73–9.86(m, pyridine)	133–138°[g]	
XII	91	C 53.04 H 3.87 N 7.74	53.43 4.23 8.00	181	1735, 1600(C=O)	4.18(s, OCH_3); 9.68–9.76(m, pyridine)	216–218°	
XIII	20			129[d]	1750, 1640(C=O)	3.44(s, NCH_3); 3.78(s, OCH_3); 1.70–2.80(m, CH_2)		
XIV	80			129[h]	1735, 1710(C=O)	3.82(s, OCH_3); 1.83–2.83(m, CH_2)		6
XV	31			169[d]	1730, 1575(C=O)	3.45(s, NCH_3); 3.78(s, OCH_3); 1.10–2.90(m, cyclohexane)	78–80°	
XVI	85			169[h]	1739, 1705(C=O)	3.77(s, OCH_3); 1.20–2.90(m, cyclohexane)	94–96° (lit. 96°)	7

[a] Schwarzkopf Microanalytical Laboratories, Woodside, N.Y. [b] The solvent was trifluoroacetic acid. [c] The reference was sodium 2,2,3,3-tetradeutero-3-(trimethylsilyl)propionate. [d] The number represents the OH-cleaved molecular ion M^+ (*m/e*) of the corresponding acid-ester which, in turn, was formed by the cleavage of the trimethylhydrazonium cation and abstraction of a hydrogen. [e] The frequency values listed here are for the recrystallized sample and differ somewhat from those reported previously (1). [f] Same as *d* but no OH cleavage. [g] The melting range is for the solvent-washed product whose recrystallization from various solvents was unsuccessful; it became oily. [h] Molecular ion minus 17 (OH).

data, and for those acid-esters that had not been reported previously.

Because of high reactivity inherent to ester groups, the acid-esters offer a wide applicability in the synthesis of biologically active substances. For example, hydrazides analogous to currently used drugs, isoniazid or isocarboxazid, can easily be prepared from these acid-esters. Such hydrazides, however, due to their amphoteric character, would be considered unique.

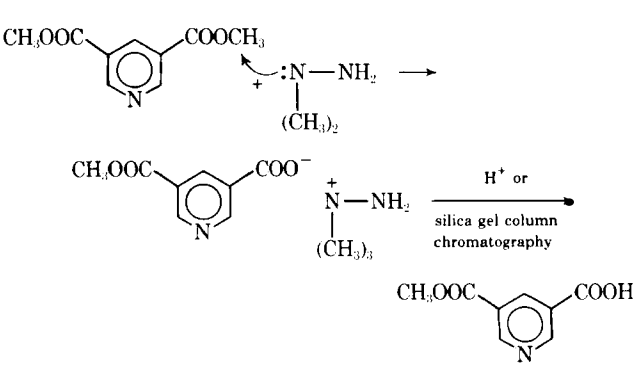
EXPERIMENTAL[3]

A general procedure for the synthesis of the acid-esters and their precursor trimethylhydrazonium esters is exemplified by the experimental procedures described for XI and XII. An additional description is given for the reaction procedure of dimethyl 2,3-pyridinedicarboxylate, since it was somewhat different from that of the general procedure.

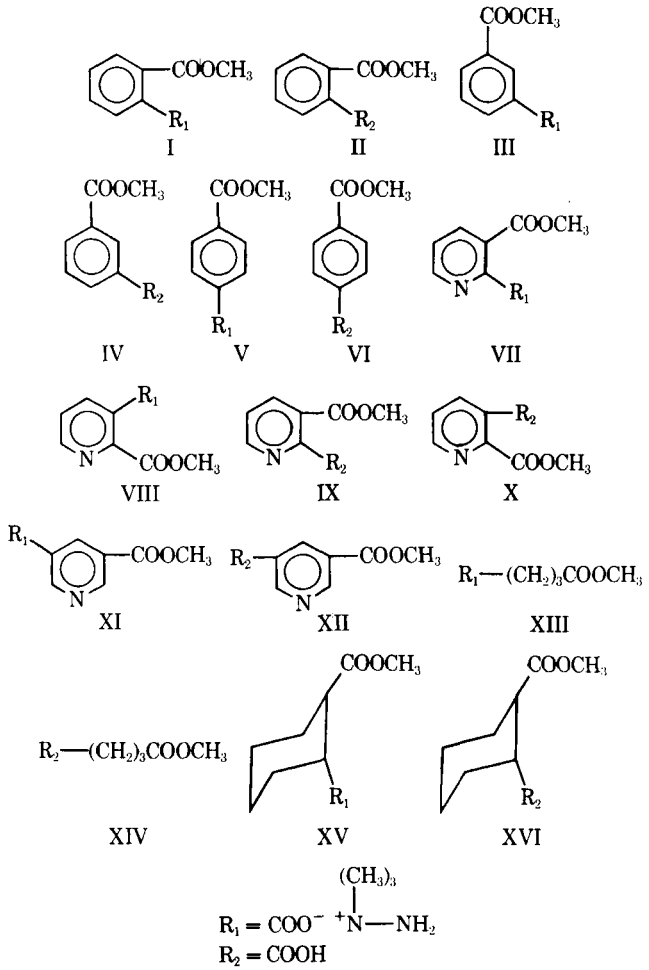
[3] The melting points were determined in a Thomas-Hoover Uni-Melt apparatus, using open capillaries, and are uncorrected. The IR spectra were determined on a Beckman IR-8, using KBr disks for the solid compounds *and a sodium chloride* window sandwich for the semisolid and liquid compounds. Only the bands for N—H and C=O stretching frequencies (ν_{max}) in reciprocal centimeters were reported. The NMR spectra were determined on a Jeol C-60 HL, using trifluoroacetic acid as a solvent and sodium 2,2,3,3-tetradeutero-3-(trimethylsilyl)propionate as a reference. The peak positions were reported in parts per million (δ); s and m designate singlets and multiplets, respectively. The mass spectra were determined on a DuPont 21-491, and only the parent ions (*m/e*) are reported. The TLC was done on microscope slides coated with silica gel (HF 254+366, Brinkmann Instruments, Inc.).

Trimethylhydrazonium 5-Carbomethoxy-3-pyridinecarboxylate (XI)—To 0.5 g (0.002 mole) of dimethyl 3,5-pyridinedicarboxylate was added 3.0 g (0.05 mole) of 1,1-dimethylhydrazine. The mixture was heated under reflux for 6 hr. After cooling to room temperature, the reaction product, whose formation was observed by TLC, was washed successively with ether and carbon tetrachloride to eliminate the unreacted ester and the excess 1,1-dimethylhydrazine. Removal of solvent *in vacuo* afforded 0.4 g of XI (60%).

5-Carbomethoxy-3-pyridinecarboxylic Acid (XII)—To 0.40 g (0.0016 mole) of XI was added, dropwise, sufficient 5% HCl to effect its dissolution. After 10 min at room temperature, the solu-



Scheme I



tion gave a precipitate[4] of XII which, on filtration and drying *in vacuo*, weighed 0.26 g (91%). It was characterized by IR, NMR, and mass spectrometry. The sample for elemental analysis was crystallized once from a mixture of about 1% methanol in benzene.

Trimethylhydrazonium 3-Carbomethoxy-2-pyridinecarboxylate (VII) and Trimethylhydrazonium 2-Carbomethoxy-3-pyridinecarboxylate (VIII)—To 5.0 g (0.026 mole) of dimethyl 2,3-pyridinedicarboxylate was added 12.0 g (0.2 mole) of 1,1-dimethylhydrazine. The mixture was left at room temperature for 24 hr, at which time a gummy substance was formed. Washing successively with ether and carbon tetrachloride eliminated the unreacted ester and 1,1-dimethylhydrazine. The residue was dried under vacuum to give 1.5 g (23%) of a mixture of VII and VIII, as determined by IR, NMR[5], and mass spectrometry. Attempts to separate the two isomers by differential solubility and chromatography were unsuccessful.

3-Carbomethoxy-2-pyridinecarboxylic Acid (IX) and 2-Carbomethoxy-3-pyridinecarboxylic Acid (X)—A crude mixture (1.5 g, 0.006 mole) of VII and VIII in 5 ml methanol was chromatographed on a column containing 25 g silica gel, and was developed with 15% methanol in methylene chloride. The fourth 10-ml fraction of the eluate gave a small quantity of the unreacted diester. The combined fifth to 12th fractions contained 0.2 g (20%) of a mixture of IX and X. The individual acid-esters were separated from the mixture by differential solubility in ethyl acetate and identified by comparing their spectral data with those of the authentic samples prepared by a method described by Kenyon and Thaker (5).

REFERENCES

(1) J. Nematollahi, *J. Heterocycl. Chem.*, **9**, 963(1973).

(2) E. Eliel and A Burgstahler, *J. Amer. Chem. Soc.*, **71**, 2251(1949).

(3) A. Wohl, *Chem. Ber.*, **43**, 3474(1910).

(4) S. Cohen and H. Smith de Pennington, *J. Chem. Soc.*, **113**, 57(1918).

(5) J. Kenyon and K. Thaker, *J. Chem. Soc.*, **1957**, 2531.

(6) "The Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa.

(7) M. Vavon and P. Peignier, *Bull. Soc. Chem. Fr.*, **45**, 293(1929).

ACKNOWLEDGMENTS AND ADDRESSES

Received December 17, 1973, from the *College of Pharmacy, University of Texas at Austin, Austin, TX 78712*

Accepted for publication March 6, 1974.

The authors express appreciation to Dr. Philip Stotter, Chemistry Department, University of Texas, for discussions and suggestions in regard to this investigation.

[x] To whom inquiries should be directed.

[4] For acid-esters that were liquid or that would not precipitate upon addition of hydrochloric acid, ether extraction and/or silica gel column chromatography (described for IX and X) were used.

[5] Two peaks of about 3:1 ratio (δ 4.20 and 4.18, respectively) for OCH_3 protons were indicative of the presence of a mixture of VII and VIII.