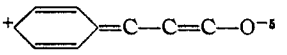
trum and the spectra of related enol-ethers and chalcones. Nevertheless, it is observed[4] that (1) the isomeric enol-ethers can have almost identical spectra (compounds 3 and 4), (2) the *cis* and *trans* forms of an enol-ether have very different spectra (compounds 17 and 18), (3) the $\lambda_{max.}$ of an enol-ether is quite different from that of the enol or the related chalcone, and (4) the diketones containing substituents in the ortho positions of the phenyl ring have $\lambda_{max.}$ less than 335 mμ and of relatively low intensity (compounds 2, 9 and 16).

It may be assumed that the main chromophoric system in the chalcones is C_6H_5–C=C–C=O, probably due to the resonant form



Thus, any group attached to the phenyl ring which readily accepts the positive charge, such as an alkoxyl group, will have a bathochromic effect while negative groups (NO_2, COOH, etc.) will have the opposite effect. Non-resonating groups, such as the methyl group, will have only a small influence on $\lambda_{max.}$. These expectations are found to be true, in general, upon inspection of the $\lambda_{max.}$ listed in Table II.[6] The third column gives the difference from the $\lambda_{max.}$ of the unsubstituted benzalacetophenone.

(4) The authors are indebted to an unknown referee for a part of the view-point presented here.

(5) Compare discussion by Katzenellenbogen and Branch, THIS JOURNAL, **69**, 1615 (1947).

Experimental

The absorption measurements were made using a Beckman Photoelectric Quartz Spectrophotometer, Model DU, with 1-cm. square, fused silica, absorption cells. Ninety-five per cent. ethanol served as the solvent. All of the compounds were prepared by students and their analyses agreed with the calculated values.

Summary

The spectra of several 1,3-diketones, Ar_1–CO–CH_2–CO–Ar_2, and of related enol-ethers, Ar_1–CO–CH=C(OCH_3)–Ar_2, and chalcones, Ar_1–CO–CH=CH–Ar_2, have been measured and the wave length, $\lambda_{max.}$, of their maximum absorption bands are herein reported. Several observations are made and discussed regarding the $\lambda_{max.}$ of the enol-ethers and of chalcones containing very different groups Ar_1 and Ar_2.

(6) Additional examples may be found among the spectra reported by Alexa for a large number of substituted chalcones, V. Alexa, *Bul. Chim., Soc. Chim. România*, [2] **1**, 77 (1939).

WASHINGTON, D. C. RECEIVED APRIL 30, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Synthesis and Investigation of Pyridine and Pyrazine Analogs of Salicylates[1,2]

BY LEWIS R. FIBEL[3] AND PAUL E. SPOERRI

The pyridine hydroxycarboxylic acids, as contrasted with their benzene analogs, are not adequately described in the literature. Some of them were therefore synthesized and their properties investigated.

As representative of heterocyclic analogs of salicylic acid, we have prepared 2-hydroxynicotinic acid, 3-hydroxypicolinic acid, chelidamic acid (4-hydroxypyridine-2,6-dicarboxylic acid) and 3-hydroxypyrazinoic acid. We also synthesized 2-mercaptonicotinic acid, analogous to thiosalicylic acid.

Tautomerism of the hydroxyl group would lead to a carbonyl configuration, as has been shown in 2-hydroxypyridine–α-pyridone. Standard procedures were applied to 2-hydroxynicotinic acid in attempts to produce the oxime, phenylhydrazone, *p*-nitrophenylhydrazone, and 2,4-dinitrophenylhydrazone, but all the attempts were unsuccessful. Analogous heterocyclic carbonyl groups directly attached to the ring rarely form oximes or hydrazones.[4]

3-Aminopicolinic acid has been prepared by the Hofmann degradation of quinolinic imide or amide. Sucharda[5] used the action of sodium hypochlorite on the imide. Ochiai and Arai[6] used hypobromous acid on the imide, and Kirpal,[7] sodium hypobromite on quinolinic acid α-amide. We obtained best results using sodium hypobromite on the imide.

From chelidamic acid, we prepared dimethyl chelidamate by the usual esterification procedure using methanol and sulfuric acid. It was obtained as the monohydrate and, on saponification, chelidamic acid was regenerated. Meyer[8] prepared what he claimed to be dimethyl chelidamate by the action of diazomethane on chelidamic acid.

By the action of diazomethane on chelidamic

(1) Presented in part at the meeting of the American Chemical Society, New York, September 15–19, 1947.

(2) Abstracted from the dissertation presented to the Graduate Faculty by Lewis R. Fibel in partial fulfilment of the requirements for the Ph.D. degree, June, 1947.

(3) Present address: W. M. Grosvenor Laboratories, Inc., 50 East 41st Street, New York, N. Y.

(4) Exceptions are noted by Petrenko-Kritschenko and Mosseschwili, *J. prakt. Chem.*, [2] **64**, 496 (1901); Bedekar, Kaushal and Deshapande, *J. Indian Chem. Soc.*, **12**, 465 (1935); and Cawley and Plant, *J. Chem. Soc.*, 1214 (1938).

(5) Sucharda, *Ber.*, **58**, 1727 (1925).

(6) Ochiai and Arai, *J. Pharm. Soc. Japan*, **59**, 458 (1939); *C. A.*, **34**, 108 (1940).

(7) Kirpal, *Monatsh.*, **29**, 228 (1908).

(8) H. Meyer, *ibid.*, **26**, 1311 (1905); **25**, 1193 (1904).

acid, we obtained dimethyl N-methylchelidamate, which on saponification yielded N-methylchelidamic acid. This acid has been previously prepared in an impure state by Haitinger and Lieben[9] and Riegel and Reinhard.[10]

In view of the success of Ewing and Steck[11] in interpreting the absorption spectra of hydroxyquinolines in terms of the configuration of the oxygen atom, we have measured the absorption spectra of these acids and of their methyl esters in alcoholic, acid and alkaline solution. However, we have found that the carboxyl group has a greater sensitivity to *p*H than the hydroxyl group, and therefore masks the effect of the latter in the absorption spectra.

Experimental[12]

2-Hydroxynicotinic Acid.—8-Hydroxyquinoline was oxidized to quinolinic acid with fuming nitric acid according to the methods of Sucharda[5] and Linstead, Nobel and Wright.[13] The acid was converted to the anhydride by the action of acetic anhydride by the method of Philips[14] and Dox.[15] Quinolinic acid α-monoamide was prepared by a modification of the method of Philips.[14] A solution of 37 g. of quinolinic anhydride in 500 ml. of methyl ethyl ketone was treated with ammonia gas. The white precipitate which formed was filtered off at intervals, and the filtrate again treated with ammonia until no further precipitation occurred. Treatment for four half-hour periods was required. The solid was washed with water. The insoluble material is the monoamide, an additional quantity of which can be obtained by acidification of the filtrate. The total yield was 21.6 g., m. p. 176° (dec.).

The amide was converted to 2-aminonicotinic acid by the Hofmann degradation, and this was converted into 2-hydroxynicotinic acid by diazotization, and boiling of the diazonium solution. This is essentially according to Philips[14] and Dornow and Karlson.[16] The acid was obtained in 71% yield as silky white needles that melted at 255° without decomposition. The methyl ester was obtained by the action of methanol and sulfuric acid on the acid; on recrystallization from benzene, it was obtained as clusters of small white needles, m. p. 142–143°.

Anal. Calcd. for $C_7H_7O_3N$: N, 9.15. Found: N, 9.30.

2-Mercaptonicotinic Acid.—2-Chloronicotinic acid was prepared as suggested by Seide.[17] 2-Hydroxynicotinic acid (6.6 g., 0.047 mole), 9.8 g. (0.047 mole) phosphorus pentachloride and 7.4 g. (0.047 mole) phosphorus oxychloride were heated under reflux for one hour at 135–140°. The resulting dark amber solution was poured onto 100 g. of ice, and after standing overnight, the precipitated solid was filtered off, washed with water and dried for two hours at 105°. There resulted 6.0 g. (81% of theory) of a white solid, m. p. 185°. A sample recrystallized from water melted at 190–191°.

2-Mercaptonicotinic acid was prepared by a modification of the method of Sucharda and Troszkiewicz.[18] In a stainless steel bomb were placed 3.15 g. (0.02 mole) of 2-chloronicotinic acid and 25 ml. (0.035 mole) of 1.4 *M* aqueous-alcoholic sodium hydrosulfide, and the bomb was heated for six hours at 130–140°. The brown liquid obtained was evaporated on the steam-bath to a small volume, and neutralized with acetic acid. The precipitate was washed with water and dried at 50°. There resulted 3.08 g. (98%) of a yellow solid, m. p. 256° (dec.). A sample was recrystallized twice from ethanol; bright yellow, fine needles, m. p. 260–261° (dec.).

Anal. Calcd. for $C_6H_5O_2NS$: N, 9.03. Found: N, 8.93.

The methyl ester was obtained by the action of methanol and sulfuric acid on the acid; after purification, white crystalline solid m. p. 204°.

Anal. Calcd. for $C_7H_7O_2NS$: N, 8.28. Found: N, 8.40.

3-Hydroxypicolinic Acid.—Quinolinic imide was prepared from quinolinic anhydride and acetamide following the method of Sucharda[5] for the preparation of the imide from quinolinic acid. Thirty three grams (0.236 mole) of quinolinic imide was dissolved in a solution of 38 g. (0.94 mole) of sodium hydroxide in 720 ml. of water, treated with a solution containing 0.519 mole of sodium hypobromite, and then heated on the steam-bath for ninety minutes. The solution was acidified to *p*H 5 with acetic acid and evaporated to about one-third volume. On cooling, there was obtained 8 g. (24.5%) of 2-aminonicotinic acid. The filtrate was treated with 375 ml. of saturated cupric acetate solution and the precipitated copper salt of aminopicolinic acid was filtered off, and washed well with water. The washed salt was suspended in water and treated with hydrogen sulfide. The precipitated cupric sulfide was filtered off and washed, and the combined filtrate and washings were, after decolorizing with charcoal, evaporated to dryness. There was thus obtained 13 g. (40%) of 3-aminopicolinic acid, m. p. 201–202° (dec.); on purification, the compound melted at 210–214°.

3-Hydroxypicolinic acid was prepared according to Kirpal[7] by the diazotization of aminopicolinic acid and boiling the solution of the diazonium salt. From this solution the copper salt of the hydroxypicolinic acid was precipitated by the addition of saturated cupric acetate solution and after isolation and washing the copper salt, the free acid was obtained by the action of hydrogen sulfide. The crude acid was recrystallized twice from methanol, and was obtained as glistening white needles, m. p. 214–215° (dec.).

Anal. Calcd. for $C_6H_5O_3N$: N, 10.07. Found: N, 10.14.

Chelidamic Acid.—Chelidonic acid was prepared by the method of Riegel and Zwilgmayer[19] by the condensation of acetone and ethyl oxalate. Chelidonic acid was treated with aqueous ammonia solution to produce chelidamic acid as described by Lerch,[20] Haitinger and Lieben,[9] and Riegel and Reinhard.[10] After recrystallization twice from 200 volumes of water using charcoal, chelidamic acid was obtained as the monohydrate, shining white fine prisms, m. p. 247–248° (dec.). The dimethyl ester was obtained by the action of methanol and sulfuric acid on the acid; recrystallized twice from water, the ester formed white needles of the monohydrate, m. p. 165°.

Anal. Calcd. for $C_9H_9O_5N\cdot H_2O$: C, 47.2; H, 4.80; CH_3O, 27.1. Found: C, 46.96, 47.23; H, 4.85, 5.10; CH_3O, 27.0.

The ester was saponified by refluxing one hour with *M* sodium hydroxide. Chelidamic acid was obtained by acidification.

Two grams (0.01 mole) of chelidamic acid was suspended in 50 ml. of dry ether, cooled in an ice-water-bath, and treated with a diazomethane solution prepared from 5.0 g. (0.04 mole) of nitrosomethylurea. After standing thirty minutes, the ether was evaporated and unreacted chelidamic acid was extracted from the residue with dilute sodium bicarbonate solution. The residue was recrystallized from water, feathery white needles, m. p. 128–129°. This compound is believed to be identical with that pre-

(9) Haitinger and Leiben, *ibid.*, **6**, 279 (1885).

(10) Riegel and Reinhard, THIS JOURNAL, **48**, 1344 (1926).

(11) Ewing and Steck, *ibid.*, **68**, 2181 (1946).

(12) All melting points are uncorrected. Microanalyses were performed by Dr. Francine Schwarzkopf, Elmhurst, L. I.

(13) Linstead, Noble and Wright, *J. Chem. Soc.*, 1911 (1937).

(14) Philips, *Ann.*, **288**, 253 (1895); *Ber.*, **27**, 840 (1894).

(15) Dox, THIS JOURNAL, **37**, 1949 (1915).

(16) Dornow and Karlson, *Ber.*, **73**, 544 (1940).

(17) Seide, *Ber.*, **57**, 1805 (1924).

(18) Sucharda and Troszkiewicz, *Roczniki Chem.*, **12**, 493 (1932).

(19) Riegel and Zwilgmayer, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, New York, N. Y., 1943, p. 126.

(20) Lerch, *Monatsh.*, **5**, 383 (1884).

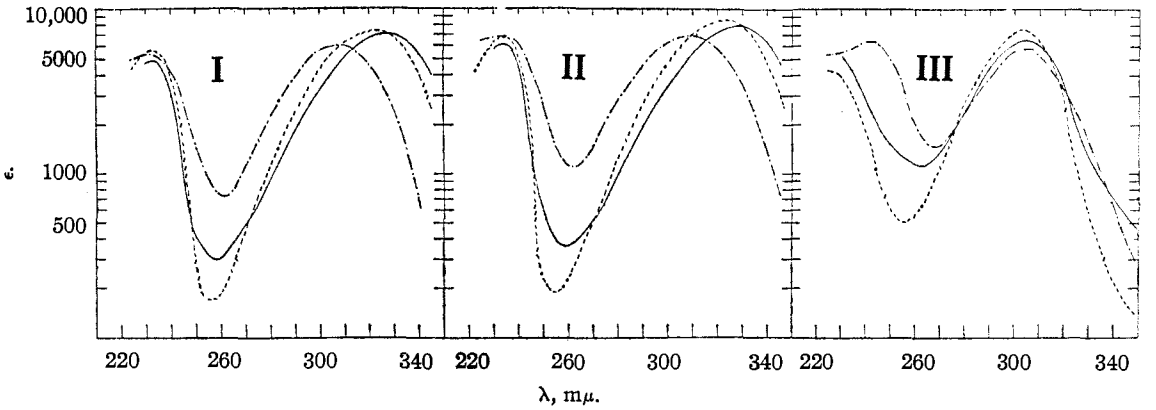


Fig. 1.—Spectra of 2-hydroxynicotinic acid (I), methyl 2-hydroxynicotinate (II), and 3-hydroxypicolinic acid (III): — ethanol, ---- hydrochloric acid, ——— sodium hydroxide.

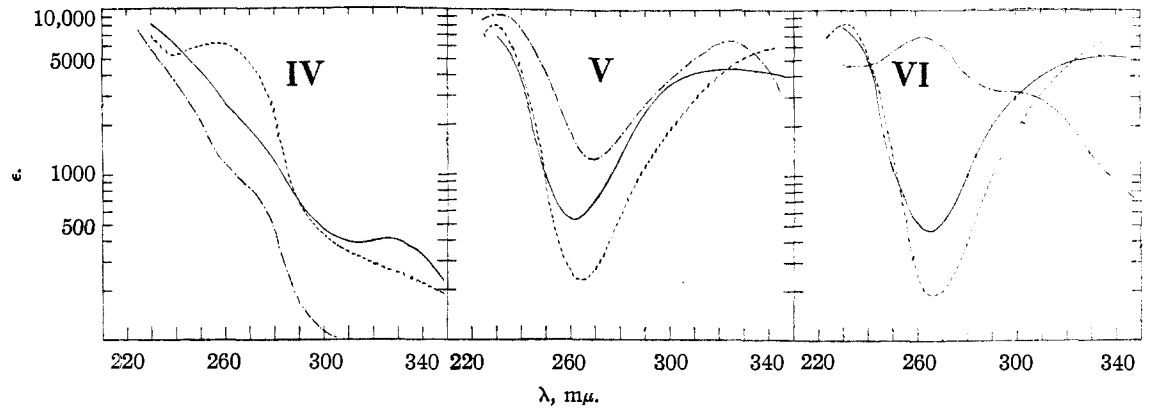


Fig. 2.—Spectra of N-methylchelidamic acid (IV), 3-hydroxypyrazinoic acid (V), and methyl 3-hydroxypyrazinoate (VI): — ethanol, ---- hydrochloric acid, ——— sodium hydroxide.

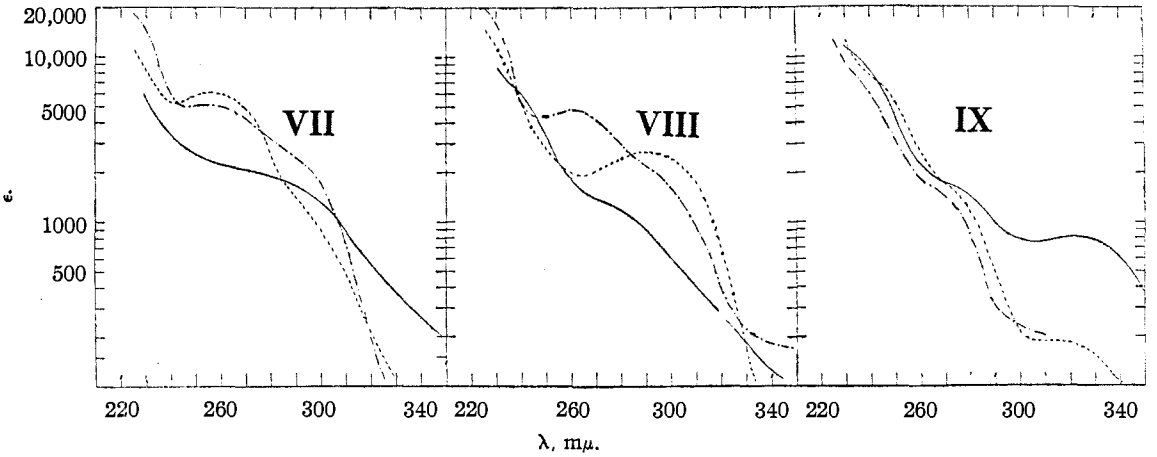


Fig. 3.—Spectra of chelidamic acid monohydrate (VII), dimethyl chelidamate monohydrate (VIII), and dimethyl N-methylchelidamate (IX): — ethanol, ---- hydrochloric acid, ——— sodium hydroxide.

pared by Meyer,[8] and was shown by analysis to be dimethyl N-methylchelidamate, not dimethyl chelidamate as he reported.

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.3; H, 4.89. Found: C, 53.43; H, 5.07.

The structure of this compound was further proved by saponification. On acidification there was obtained N-methylchelidamic acid, m. p. 224° (dec.).

Anal. Calcd. for $C_8H_7O_5N \cdot H_2O$: C, 44.65; H, 4.19. Found: C, 44.45; H, 4.19.

A sample was recrystallized from water, white rosettes, m. p. 225–226° (dec.). For analysis, a sample was dried

to constant weight at 136°, and then again combusted.

Anal. Calcd. for $C_6H_7O_5N$: C, 48.75; H, 3.55. Found: C, 48.75; H, 3.58.

3-Hydroxypyrazinoic Acid.—3-Aminopyrazinoic acid was prepared according to the method of Weijlard, Tishler and Erickson.[21] 3-Hydroxypyrazinoic acid was prepared by the method of Erickson and Spoerri[22] by the action of nitrosyl sulfuric acid on 3-aminopyrazinoic acid at 0°. We have also prepared 3-hydroxypyrazinoic acid by the following method. 3-Aminopyrazinoic acid (6.95 g., 0.05 mole) was dissolved by heating in a mixture of 55 ml. of water and 55 ml. of 3.75 *M* sulfuric acid. The solution was cooled to 12°, and then treated dropwise with 18.5 ml. (0.06 mole) of 3.3 *M* sodium nitrite. The temperature was maintained at 10–17° over the twenty-minute period of addition. Stirring was continued for half an hour while being heated to boiling. The mixture was cooled to room temperature, and the solid filtered off, and extracted with dilute sodium bicarbonate solution. The solution was acidified to precipitate hydroxypyrazinoic acid. There resulted 4.69 g. (67%), decomposing at 230° without melting. The acid was recrystallized from water using charcoal, yellow crystalline solid, decomposing at 223–225° without melting.

The **methyl ester** was prepared from the acid and methanol and sulfuric acid. After purification, it was obtained as a slightly yellow crystalline solid, m. p. 148–149°.

Anal. Calcd. for $C_6H_6O_3N_2$: N, 18.17. Found: N, 17.92.

Spectrophotometry.—Riegel and Reinhard[10] have previously measured the spectra of chelidamic and N-methylchelidamic acids. Otherwise the spectra of these compounds have not been published. The general method of investigation followed very closely the technique of Ewing and Steck[11] for hydroxyquinolines. The samples used for measurement of spectra were those prepared for analysis. Each compound was run in U.S.P. 95% ethanol, in 0.02 *M* sodium hydroxide, and in 0.02 *M* hydrochloric acid. Methyl 2-mercaptonicotinate was too insoluble in water to use aqueous solutions of acid and alkali. In this case, an acid solution was prepared by diluting 2.5 ml. of 1.0 *M* aqueous hydrochloric acid to 250 ml. with 95% ethanol. The alkaline solution was prepared by dissolving the weighed compound in 95% ethanol, adding 1.0 ml. of 1.0 *M* sodium hydroxide, and diluting to 100 ml. with 95% ethanol. In each case, the solvent used as a blank was of the same batch as that used to dissolve the sample. The solvents had the following *p*H: ethanol, 6–7; hydrochloric acid, 2–3; and sodium hydroxide, 11–12. Concentrations varied from 9 to 35 mg. per liter. The instrument used for the measurements was a Beckman Model DU quartz spectrophotometer.[23] The spectra are shown in Figs. 1–4, in which the molecular extinction coefficient, ϵ, is plotted semi-logarithmically against the wave length, λ, in mμ.

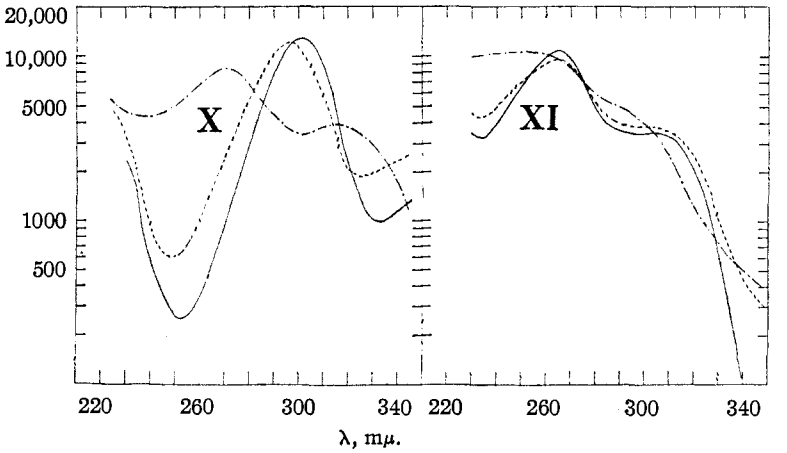


Fig. 4.—Spectra of 2-mercaptonicotinic acid (X), and methyl 2-mercaptonicotinate (XI): — ethanol, --- hydrochloric acid, ——— sodium hydroxide.

Summary

1. Chelidamic acid, 2-hydroxynicotinic acid, 2-mercaptonicotinic acid, 3-hydroxypicolinic acid, and 3-hydroxypyrazinoic acid have been prepared by improvements on known procedures.

2. The methyl esters of these acids, except 3-hydroxypicolinic acid, have been prepared. These esters are not previously described in the literature.

3. The N-methyl derivative of dimethyl chelidamate has been prepared. It was previously incorrectly reported as dimethyl chelidamate.

4. Spectrophotometric observations of these acids and esters are reported.

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(21) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 802 (1945).

(22) Erickson and Spoerri, *ibid.*, **68**, 400 (1946).

(23) The instrument was the property of the Weizmann Institute of Science, Rehoboth, Palestine, and was loaned through the courtesy of Dr. K. G. Stern, to whom the authors are very grateful.