are shown in Table IV.

A plot of proton affinities against the N values of alcohols based on the pentamethyleneiodonium (N_{PW}) ion,[8] a primary substrate, reveals an earlier onset of steric retardation in the series, as expected (Figure 4). These steric retardation factors (SRF) are also shown in Table IV.[26] These values support the contention[8,9] that inversion of the nucleophilicity order in 2-octyl solvolyses[5,9] is an expected consequence of steric factors.

Correlation of N vs. Ionization Potential (IP). Dougherty[27] has previously suggested that there should be a correlation between IP and N. Bentley and Schleyer[3] showed that the correlation between experimental solvent nucleophilicities and the IP's of a wide range of hydroxylic solvents was not good. However, for limited series, IP's plot linearly vs. proton affinities (Figure 5),[28-30] and, therefore, IP's should correlate with N values for such compounds. Nevertheless, large differences in solvent electrophilicity[15] and differences in solvent bulk properties (e.g., dimerization of neat acetic acid[8]) are expected to cause correlations between gas-phase properties and solutions properties to be poor.[4] Steric factors,[31] as shown here, may also make such correlations poor.

Solvent Effects on Correlations of Basicity and Nucleophilicity. As stated earlier, correlations of nucleophilicity with solution-phase basicity have generally been poor. There have been some successes, however, when solvation differences were minimized.[32] Other than the Schadt-Bentley-Schleyer (SBS) study,[11] the data treated here were for a single functional class of nucleophiles in a single solvent. While the SBS study has moved toward the separation of solvation factors in assessing nucleophilicity, there is reason[3,4] to believe that the present treatment may be inapplicable to widely different types of nucleophiles and solvents.[33] Nevertheless, the present method is useful for quantifying steric hindrance to nucleophilicity at least over a modest range of structural differences.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Helpful comments and suggestions from E. M. Arnett, T. W. Bentley, J. M. Harris, and R. W. Taft are kindly acknowledged. Professors Arnett and J. L. Beauchamp kindly provided data prior to publication.

Registry No. 4-Cyanopyridine, 100-48-1; 3-fluoropyridine, 372-47-4; 3-chloropyridine, 626-60-8; pyridine, 110-86-1; 3-methylpyridine, 108-99-6; 3-cyanopyridine, 100-54-9; 4-acetylpyridine, 1122-54-9; 4-methylpyridine, 108-89-4; 4-methoxypyridine, 620-08-6; 2-methylpyridine, 109-06-8; 2-ethylpyridine, 100-71-0; 2-isopropylpyridine, 644-98-4; $MeOSO_2F$, 421-20-5; EtI, 75-03-6; H_2O, 7732-18-5; MeOH, 67-56-1; EtOH, 64-17-5; i-PrOH, 67-63-0; t-BuOH, 75-65-0; MeOTs, 80-48-8; pentamethyleneiodonium, 41688-68-0.

(26) Similar plots have been constructed with the N values from ref 12 and 15 with similar results; data are not available in those cases for i-PrOH and t-BuOH; therefore, they add nothing to this discussion.

(27) Dougherty, R. C. *Tetrahedron Lett.* **1975**, 385.

(28) IP's were measured by PE spectroscopy: Danby, C. J.; Cocksey, B. J.; Eland, J. H. D. *J. Chem. Soc. B* **1971**, 790.

(29) Other LFER have previously been developed by several groups: cf. ref 28; Kurylo, M. J.; Jurinski, N. B. *Tetrahedron Lett.* **1967**, 1983; Henderson, W. G.; Beauchamp, J. L.; Holtz, D.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 4728; Dekock, R. L.; Barbachyn, M. R. *Ibid.* **1979**, *101*, 6415; Olmstead, W. N.; Brauman, J. I. *Ibid.* **1977**, *99*, 4219; Taft, R. W.; Wolf, J. F.; Beauchamp, J. L.; Scorrano, G.; Arnett, E. M. *Ibid.* **1978**, *100*, 1240; Levitt, L. S.; Widing, H. F. *Prog. Phys. Org. Chem.* **1976**, *12*, 119.

(30) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1972**, *94*, 4726.

(31) Steric retardation has been recently suggested as one reason for the poor nucleophilicity of some fluorinated alcohols; cf.: Bentley, T. W.; Bowen, C. T.; Parker, W.; Watt, C. I. F. *J. Am. Chem. Soc.* **1979**, *101*, 2486.

(32) Two recent articles, published after submission of this manuscript, provide dramatic evidence of steric factors on nucleophilicity and correlate nucleophilicity and solution basicity; cf.: Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1980**, *45*, 3314, 3320.

(33) Plots of $\Delta G°$ or $\Delta H°$ for solution protonation vs. PA are linear for 3- and 4-substituted pyridines but 2-substituted pyridines with polar groups in the 2-position fail to give a high correlation coefficient (ref 20). It was suggested that these deviations could be explained with field-effect theories. Such effects should not be operative with the 2-alkyl groups treated here, but one should be aware of the possibility of this competing factor with polar 2-substituents. Rate data are available for several polar 2-substituted pyridines in Me_2SO relative to the rate of pyridine (Deady, L. W.; Zoltwiez, J. A. *J. Org. Chem.* **1972**, *37*, 603). However, rates of the 3-substituted pyridine derivatives in Me_2SO have been reported relative to pyrazine (Deady, L. W.; Zoltewiez, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 5475). Converting the latter rates to values relative to pyridine, and then to N values, resulted in a relatively poor correlation of N vs. PA for the 3-substituents (R = 0.93). Therefore, we have not further treated this data. Since Deady and Zoltewiez discuss steric effects on their rates, the reader is referred to the first mentioned article.

Reaction of 2'-Hydroxychalcone Dibromides with Pyridine

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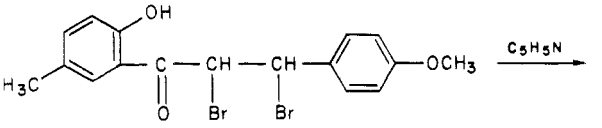
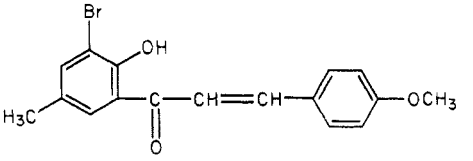
2'-Hydroxychalcone dibromides react with pyridine to give a variety of products. Thus Ghiya and Marathey[1] observed that heating 2'-hydroxy-4-methoxy-5'-methylchalcone dibromide (**1**) with pyridine gave the nuclear halogenated chalcone (**2**).



1



2

Jadhav et al.[2] studied the reactions of a large number of chalcone dibromides and found that these are converted to either α-bromochalcones, flavones, or aurones, depending upon the nature and position of the substituents in the aromatic nuclei. The formation of bromoflavones has also been reported.[3,4]

Keeping in view the products formed in this reaction, we have treated a series of variously substituted chalcone dibromides with pyridine at the boiling point. In order

(1) B. J. Ghiya and M. G. Marathey, *J. Sci. Ind. Res., Sect. B*, **20**, 41 (1961).

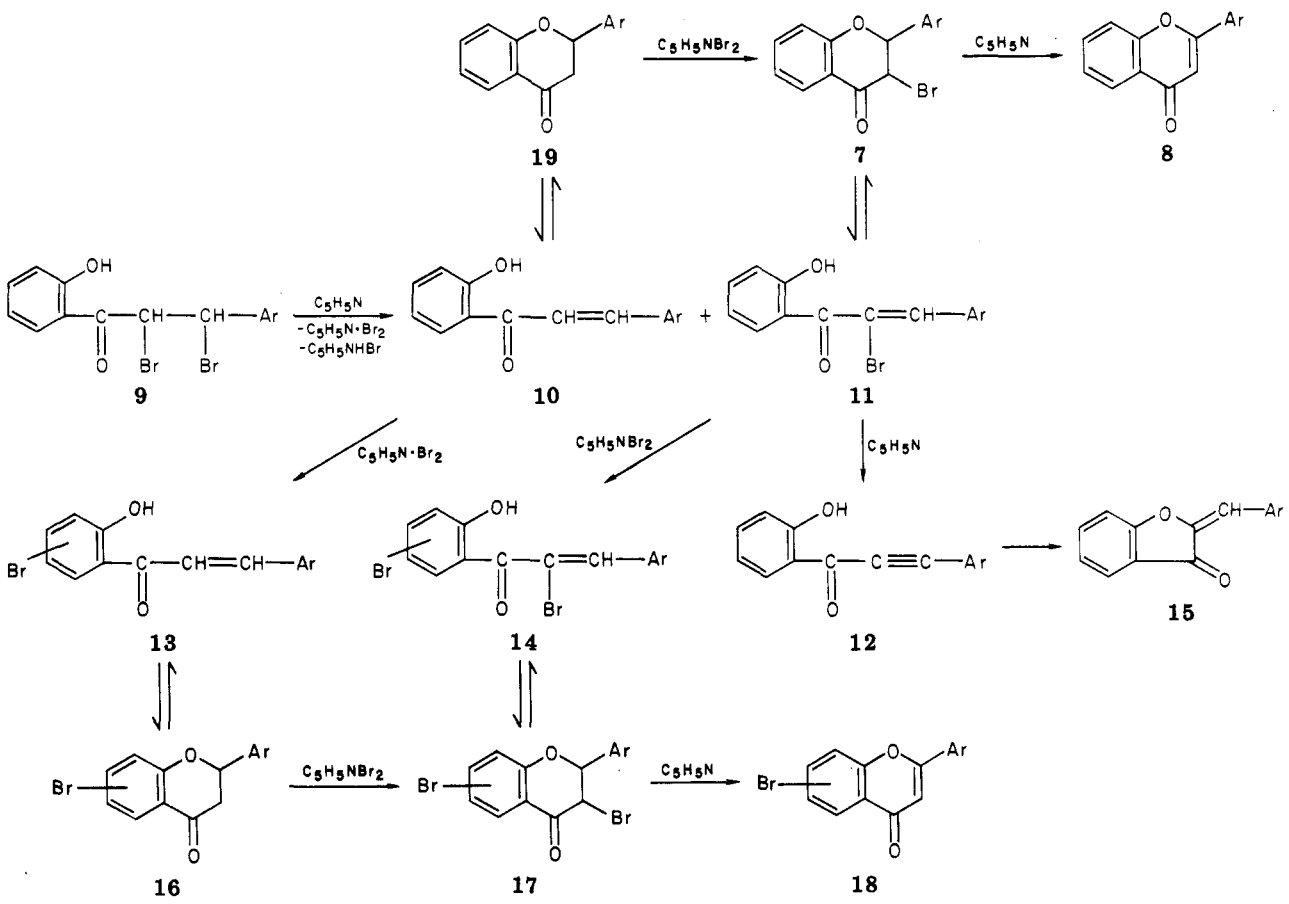
(2) F. A. Atchabba, P. L. Trivedi, and G. V. Jadhav, *J. Univ. Bombay*, **25**, 1, (1957); **27**, 8 (1958); *J. Indian Chem. Soc.*, **32**, 206 (1955).

(3) P. N. Wadodkar, *Indian J. Chem.*, 1, 163 (1963).

(4) K. R. Kutumbe and M. G. Marathey, *Chem. Ber.*, **96**, 913 (1963), and references therein.

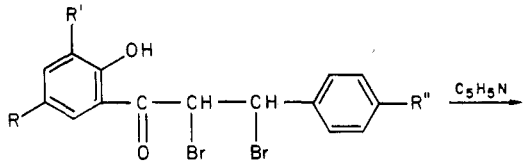
0022-3263/81/1946-0638$01.00/0

Chart I

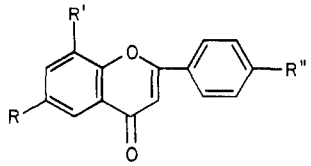


to have more insight into the reaction path, the reactions of 2′-hydroxychalcones and flavones with *N*-bromo halogenating agents, particularly those likely to be generated in the chalcone dibromide–pyridine reaction, have also been studied.

2′-Hydroxychalcone dibromide (**3a**) gave the mononuclear halogenated flavone, 6-bromoflavone (**4a**). 4-



3a, R = R′ = R″ = H
b, R = R′ = H; R″ = Cl
c, R = R′ = H; R″ = OCH_3
d, R = CH_3; R′ = H; R″ = OCH_3
e, R = R′ = Br; R″ = H
f, R = R′ = Br; R″ = Cl
g, R = R′ = Br; R″ = OCH_3
h, R = CH_3; R′ = Br; R″ = OCH_3



4a, R = Br; R′ = R″ = H
b, R = Br; R′ = H; R″ = Cl
c, R = R′ = Br; R″ = OCH_3
d, R = CH_3; R′ = Br; R″ = OCH_3
e, R = R′ = Br; R″ = H
f, R = R′ = Br; R″ = Cl

Chloro-2′-hydroxychalcone dibromide (**3b**), also unsubstituted in the 3′- and 5′-positions, gave the monobrominated compound, 6-bromo-4′-chloroflavone (**4b**) together with the unbrominated 4′-chloroflavone. 2′-Hydroxy-4-methoxychalcone dibromide (**3c**), on the other hand, gave the dihalogenated product, 6,8-dibromo-4′-methoxyflavone (**4c**).

The monohalogenated flavone, 8-bromo-4′-methoxy-6-methylflavone (**4d**), was obtained from the 5′-substituted dibromide, 2′-hydroxy-4-methoxy-5′ methylchalcone dibromide (**3d**). The chalcone dibromides substituted at both the 3′- and 5′-positions, 3′,5′-dibromo-2′-hydroxychalcone dibromide (**3e**), 3′,5′-dibromo-4-chloro-2′-hydroxychalcone dibromide (**3f**), 3′,5′-dibromo-2′-hydroxy-4-methoxychalcone dibromide (**3g**), and 5′-bromo-2′-hydroxy-4-methoxy-5′-methylchalcone dibromide (**3h**), yielded the corresponding flavones **4e**, **4f**, and **4d**, respectively.

2′-Hydroxychalcone (**5a**) reacted with pyridine perbromide, pyridine–bromine complex, and *N*-bromosuccinimide to form 3′,5′-dibromo-2′-hydroxychalcone (**6a**). Similarly, 2′-hydroxy-4-methoxychalcone (**5b**), 4-chloro-2′-hydroxychalcone (**5c**), and 2′-hydroxy-4-methoxy-5′-methylchalcone (**5d**) gave the corresponding nuclear brominated chalcones (**6b–d**).

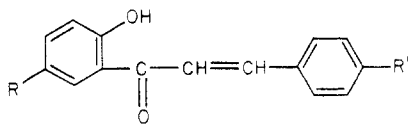
Authentic samples of 6,8-dibromo-4′-methoxyflavone (**4c**), 8-bromo-4′-methoxy-6-methylflavone (**4d**), 6,8-dibromoflavone (**4e**), and 6,8-dibromo-4′-chloroflavone (**4f**) were prepared by cyclizing the corresponding 2′-hydroxychalcone dibromides (**3e–h**) with cold aqueous ethanolic sodium hydroxide. Flavones **4c**, **4d**, **4e**, and **4h** were also prepared by the selenium dioxide oxidation of the corresponding 2′-hydroxychalcones **6b**, **6d**, **6a**, and **6c**, respectively.

A perusal of the results obtained in the present work and of those obtained by the earlier workers shows that they may be accounted for (Chart I) by the assumption that the

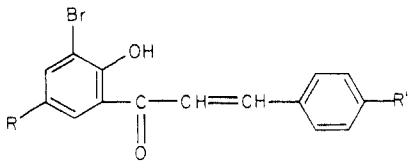
Table I

compd	recrystn solvent	mp, °C (lit. mp, °C)	% yield	anal. found, % C	H	formula	calcd, % C	H	NMR,[a] δ	mass spectrum, m/e[b]
3e	CCl_4	179-180	64	32.9	1.8	$C_{15}H_{10}Br_4O_2$	33.2	1.9		
3f	CCl_4	215-216	47	31.2	1.7	$C_{15}H_9Br_4ClO_4$	31.3	1.6		
3h	CCl_4	154-155 (156)[3]	57	40.0	2.9	$C_{17}H_{15}Br_3O_3$	40.3	3.0		
4b	C_6H_6/petroleum ether	189-190 (188-189)[8]	34	53.8	2.46	$C_{15}H_8BrClO_2$	53.7	2.4	6.7 (s, 1 H, H-3), 7.6 (m, 7 H, aromatic)	338 (15), 336 (77), 334 (65), 333 (5), 200 (52), 198 (58), 139 (44), 136 (100), 111 (61)
4c	EtOH	210-211 (205)[13]	43, 64[d]	47.0	2.8	$C_{16}H_{10}Br_2O_3$	46.9	2.5	3.68 (s, 3 H, OCH_3), 6.35 (s, 1 H, H-3), 7.3 (m, 6 H, aromatic)	412 (40), 410 (76), 408 (75), 382 (4), 380 (8), 280 (10), 278 (20), 276 (14), 199 (32), 132 (100), 105 (80)
4d	C_6H_6/petroleum ether	207-208 (192)[3]	31 64[e]	59.4	3.8	$C_{17}H_{13}BrO_3$	59.1	3.8	2.35 (s, 3 H, CH_3), 3.8 (s, 3 H, OCH_3), 6.6 (s, 1 H, H-3), 7.5 (m, 6 H, aromatic)	346 (45), 344 (56), 316 (8), 212 (81), 132 (100), 117 (83), 105 (37)
4e	EtOH	174 (174-175)[9]	83	47.1	2.1	$C_{15}H_8Br_2O_2$	47.4	2.1	5.48 (s, 1 H, H-3), 6.4 (m, 7 H, aromatic)	382 (55), 380 (100), 378 (50), 278 (33), 276 (73), 274 (37), 200 (20), 170 (6), 105 (8), 102 (67)
4f	EtOH	249-250	59	43.1	1.6	$C_{15}H_7Br_2ClO_2$	43.5	1.7		
6b	EtOH	165 (170)[13]	33	46.1	2.7	$C_{16}H_{12}Br_2O_3$	46.3	2.9		
6c	AcOH	200-201	43[c]	43.4	2.1	$C_{15}H_9Br_2ClO_2$	43.3	2.2		
6d	EtOH	148-149 (148)[1]	42[c]	59.0	4.2	$C_{17}H_{15}BrO_3$	58.8	4.3		

[a] Measured in $CDCl_3$ at 60 MHz. [b] Percentage given in parentheses. All the mass spectra obtained at 70-eV ionizing energy. [c] NBS method. [d] From **3g**. [e] From **3h**.



5a, R = R′ = H
b, R = H; R′ = OCH_3
c, R = H; R′ = Cl
d, R = CH_3; R′ = OCH_3



6a, R = Br; R′ = H
b, R = Br; R′ = OCH_3
c, R = Br; R′ = Cl
d, R = CH_3; R′ = OCH_3

first stage involved both debromination and dehydrobromination, converting the chalcone dibromide (**9**) into a chalcone (**10**) and an α-bromochalcone (**11**). Of the subsequent steps in flavone (**8**, **18**) formation, routes **11** → **8** and **11** → **18** ought to be considerably more important than routes **10** → **8** and **10** → **18** as the chalcone–flavone equilibria **11** ⇌ **7** and **14** ⇌ **17** are driven to the right by the subsequent elimination of hydrogen bromide by the base which is in large excess, while the same effect on the similar equilibria **10** ⇌ **16** and **13** ⇌ **16** requires bromination by a halogenating agent in limited supply.

Experimental Section

Melting points are uncorrected. Hydroxychalcones, dibromides,[5] and pyridine perbromide[6] were prepared by following the reported procedures unless stated otherwise.

Reaction of 2′-Hydroxychalcone Dibromide (3a) with Pyridine. The chalcone dibromide (1 g) in pyridine (10 mL) was boiled for 3 min, cooled to room temperature diluted with water, and acidified with dilute HCl. The solid which separated was collected by filtration and recrystallized from ethanol to furnish 6-bromoflavone **4a** (0.32 g, 41%): mp 191–192 °C (lit.[7] mp 191–192 °C); NMR ($CDCl_3$) δ 6.65 (s, 1 H, H-3), 7.5 (m, 7 H, aromatic), 8.15 (d, 1 H, H-5); mass spectrum, *m/e* 302 (94), 301 (30), 300 (100), 272 (10.6), 195 (97), 172 (21), 170 (24), 105 (6.6), 102 (42). Anal. Calcd for $C_{15}H_9BrO_2$: C, 59.8; H, 3.0. Found: C, 59.3; H, 3.2.

Reaction of 4-Chloro-2′-hydroxychalcone Dibromide (3b) with Pyridine. A mixture of chalcone dibromide (1 g) and pyridine (10 mL) was boiled for 3 min and allowed to cool to room temperature. The reaction mixture was then worked up as described in the previous experiment to give 4′-chloroflavone (0.12 g, 20%), mp 189–190 °C (lit.[8] mp 188–189 °C), and 6-bromo-4′-chloroflavone (**4b**) (0.27 g, 34%), mp 177–178 °C, as white needles.

Similarly, the reactions of other chalcone dibromides (**3c–h**) with pyridine were carried out and data of the reaction products are given in Table I.

(5) T. C. Sharma, V. Saxena, and N. J. Reddy, *Acta Chim. Acad. Sci. Hung.*, **93**, 415 (1977).
(6) D. M. Williams, *J. Chem. Soc.*, 2783 (1931).
(7) M. Hoshino, *Nippon Kagaku Zasshi*, **78**, 1754 (1954).
(8) W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1294 (1952).

Reaction of 2'-Hydroxychalcone with *N*-Bromosuccinimide. Formation of 3',5'-Dibromo-2'-hydroxychalcone (6a). Method A. To the chalcone **5a** (0.56 g) in dry benzene (20 mL) was added NBS (0.45 g) in an equimolar ratio. The contents were refluxed for 1 h on a water bath and allowed to cool to room temperature. The residue, after evaporation of the benzene, was washed with a little hot water to remove the succinimide. It afforded orange yellow needles of 3',5'-dibromo-2'-hydroxychalcone (**6a**) from ethanol (0.25 g, 26%), mp 143–144 °C (lit.[9,10] mp 143–144 and 145 °C). TLC showed a single spot with a benzene–petroleum ether (30:70) mixture. Anal. Calcd for $C_{15}H_{10}Br_2O_2$: C, 47.2; H, 2.6. Found: C, 46.8; H, 2.4.

The reactions of 2'-hydroxy-4-methoxychalcone (**5b**), 4-chloro-2'-hydroxychalcone (**5c**), and 2'-hydroxy-4-methoxy-5'-methylchalcone (**5d**) with NBS under the same conditions afforded **6b**, **6c**, and **6d**, respectively.

Reaction of 2'-Hydroxychalcone with Pyridine Perbromide. Formation of 3',5'-Dibromo-2'-hydroxychalcone (6a). Method B. The chalcone **3a** (0.6 g) was dissolved in acetic acid (15 mL); pyridine·perbromide (0.6 g) was added in small amounts, keeping the solution at 40–60 °C. The reaction mixture was kept at the same temperature for an additional 30 min and then allowed to stand at room temperature. After 5 days, it was diluted with water; the solid was filtered off and washed with water. Crystallization from ethanol gave orange yellow needles (0.36 g, 36%) of **6a**, mp 143–144 °C, identical in all respects with authentic material.[9,10]

Under similar reaction conditions **5b** (0.6 g), **5c** (0.8 g), and **5d** (0.7 g) reacted with pyridine perbromide to give **6b** (0.4 g, 41%), **6c** (0.46 g, 36%), and **6d** (0.47 g, 52%), respectively (see Table I).

Reaction of 2'-Hydroxychalcone with Pyridine–Bromine Complex. Bromine (0.5 mL) was added to pyridine (15 mL). To this solution was added the chalcone **3a** (2.24 g) in small quantities with shaking at room temperature. After 5 min the separated hydrobromide salt (0.36 g) was filtered off, washed with ether, and dried, mp 213–214 °C (lit.[11] mp 200 °C). The mother liquor was diluted with water and then acidified with dilute HCl. An oily compound that separated gave orange yellow needles (2.4 g, 63%) of **6a**, mp 143–144 °C from ethanol. No depression was observed in mixture melting point with the product obtained from the previous reaction.

By the same procedure **6b** (2.3 g, 57%), **6c** (2.35 g, 58%), and **6d** (1.5 g, 83%) were obtained from **5b** (2.5 g), **5c** (2.5 g), and **5d** (1.4 g), respectively.

Synthesis of 3',5'-Dibromo-2'-hydroxy-4-methoxychalcone Dibromide (3g). 3',5'-Dibromo-2'-hydroxy-4-methoxychalcone (**6b**, 1 g) was dissolved in acetic acid (50 mL) by warming on a water bath. To the hot solution was added pyridinium hydrobromide perbromide (0.8 g) and the reaction mixture was kept at room temperature for 1 h when yellowish crystals separated. These were filtered off, washed with water, and recrystallized from carbon tetrachloride to afford yellow needles of the dibromide **3g** (0.6 g, 43%), mp 172 °C (lit.[12] mp 150 °C).

Anal. Calcd for $C_{16}H_{12}Br_4O_3$: C, 33.6; H, 2.1. Found: C, 33.6; H, 1.9.

By the same procedure **3e** (0.64 g, 64%), **3f** (0.26 g, 47%), and **3h** (1.5 g, 57%) were obtained from **6a** (0.7 g), **6c** (0.4 g), and **6d** (1.8 g), respectively (see Table I).

Synthesis of 6,8-Dibromo-4'-methoxyflavone (4c). (i) 3',5'-Dibromo-2'-hydroxy-4-methoxychalcone (0.5 g) in amyl alcohol (15 mL) containing selenium dioxide (0.4 g) was refluxed at 140–150 °C for 12 h. The contents were filtered hot. The selenium was washed with a little ether. When the mother liquor was cooled, crystals of 6,8-dibromo-4'-methoxyflavone separated which were filtered off and recrystallized from ethanol to furnish white needles (0.3 g, 60%), mp 211 °C (lit.[13] mp 205 °C).

Similarly, **4e** (0.29 g, 65%), **4f** (0.31 g, 62%), and **4d** (0.31 g, 64%) were synthesized from **6a** (0.45 g), **6c** (0.5 g), **6d** (0.5 g), respectively.

(ii) The chalcone dibromide (0.5 g) was suspended in ethanol (10 mL) at room temperature and aqueous NaOH (10 M, 2 mL) was added. After 3 h the reaction mixture was acidified. The solid that separated was filtered off, washed with water, and crystallized from ethanol to give tiny white needles of 6,8-dibromo-4'-methoxyflavone (**4g**) (0.21 g, 59%) from ethanol, mp 210–211 °C. No depression in mixture melting point was observed with the previous product.

Under the same reaction conditions **3e**, **3f**, and **3h** (0.5 g of each) gave **4e** (0.21 g, 60%), **4d** (0.18 g, 53%), and **4f** (0.23 g, 65%), respectively.

Reaction of Flavone with Pyridine Perbromide. To flavone (0.3 g) in acetic acid (20 mL) at 40–60 °C was added pyridine perbromide (0.3 g) in small quantities. After 1 h the mixture was allowed to stand at room temperature for 5 days. It was then diluted with water to yield a white solid, which was filtered off and washed with water. Crystallization from ethanol gave 6-bromoflavone **4a** as white crystals (0.15 g, 37%), mp 190–191 °C. By the same procedure 4'-methoxy-6-methylflavone (0.3 g) gave **4d** (0.16 g, 41%), mp 207–208 °C. Co-TLC with an authentic sample[3] showed single spots with benzene–ethyl acetate (80:20).

Acknowledgment. We are grateful to Dr. R. P. Sharma, University of Southampton, England, and authorities of Chemistry Department, IIT Kanpur, for providing spectroscopic and analytical data. We thank UGC, New Delhi, for the award of a Junior Research Fellowship to one of us (N.J.R.).

Registry No. 3a, 39729-11-8; **3b**, 43016-14-4; **3c**, 39729-17-4; **3d**, 22129-40-4; **3e**, 10372-55-1; **3f**, 75767-98-5; **3g**, 10372-59-5; **3h**, 29976-70-3; **4a**, 1218-80-0; **4b**, 75767-99-6; **4c**, 75780-70-0; **4d**, 29976-78-1; **4e**, 42079-81-2; **4f**, 75768-00-2; **5a**, 1214-47-7; **5b**, 3327-24-0; **5c**, 3033-96-3; **5d**, 16635-13-5; **6a**, 15482-67-4; **6b**, 75780-71-1; **6c**, 75768-01-3; **6d**, 29976-66-7; 4'-chloroflavone, 10420-75-4; flavone, 525-82-6; 4'-methoxy-6-methylflavone, 29976-77-0.

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Constituents of *Trichilia hispida* (Meliaceae). 3. Structures of the Cytotoxic Limonoids: Hispidins A, B, and C

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Limonoids, a group of highly oxidized triterpenoids, are known to occur in the Meliaceae family.[1-4] In this paper, the structure determinations of three limonoids of *Trichilia hispida* (Meliaceae), hispidins A (**1**), B (**2**), and C (**3**), whose isolation was previously described,[5] are reported.

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