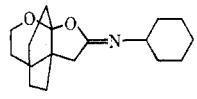
(13) Reaction with *t*-BuOK in *t*-BuOH gave imino lactone I in 76% yield. Compare ref 12.



I

(14) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969).

(15) Melting points are uncorrected. Ultraviolet spectra were measured on a Cary 14 instrument. Infrared spectra were taken on Perkin-Elmer 251 instrument. ^{1}H NMR spectra were taken in CCl_4 solutions for neutral materials or in deuteriochloroform for salts and are in δ values.

(16) Olefins and ethers are purified on distillation over Na. Merck Art 1097 activity II–III Al_2O_3 was used for the column chromotography. Dry solvent was obtained by distillation over P_2O_5 and filtration over a 100-fold amount of basic Al_2O_3 (activity I, Merck).

(17) The formation of a mass M − 166 as base peak in propellanes **42** and **48–50** was noted.

Reactions of Phthalaldehyde with Ammonia and Amines

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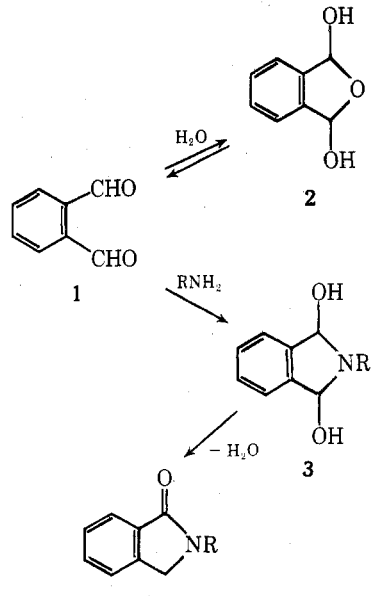
Reactions of phthalaldehyde with ammonia and amines are described. Major products from ammonia were phthalimidine and 3-(2-cyanophenyl)isoquinoline. Primary amines reacted with 2 mol of aldehyde to produce N-substituted adducts whose steric requirements lead to unusual NMR spectra. At elevated temperatures unidentified colored materials were formed. 1-Hydroxyisoindoles are proposed intermediates.

The reaction between phthalaldehyde and ammonia produces colored polymeric[1-3] products. These reactions have served as a basis for polarographic methods for the determination of ammonia[3] and for the location of sweat pores in the skin.[4] Similar reactions of phthalaldehyde with various primary amines, amino acids, and indoles also produce dark-colored products. Qualitative and semiquantitative methods for the detection of these nitrogen-containing materials depend on the fluorescence of their condensation products with phthalaldehyde.[5-7]

Preliminary to an investigation of the colored products, a study of these reactions under carefully controlled conditions was made.

Results

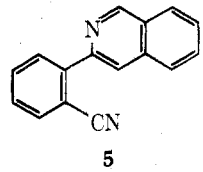
At room temperature water reacts reversibly with phthalaldehyde (1) to produce a hydrate[8] which was shown by NMR to have the structure **2**; phthalaldehyde was recovered unchanged by evaporating the solution to dryness. By contrast, the reaction with ammonia is not reversible. In cold dilute dimethyl sulfoxide (Me_2SO) an adduct formed which had an NMR spectrum consistent with **3a**. The initially formed product dehydrated and rearranged to phthalimidine (**4a**), identified by comparison to an authentic sample.[9] The diol **3a**, precipitated from dry ether at −70 °C, was very unstable and resinified rapidly when warmed to room temperature.



1 2 3 4

a, R = H
b, R = Me
c, R = Ph
d, R = 2,6-Me_2Ph

The products from the reaction of phthalaldehyde and ammonia in Me_2SO depended on the initial concentration of aldehyde. While phthalimidine (**4a**) was produced in high yield in dilute Me_2SO solutions, more concentrated solutions yielded 3-(2-cyanophenyl)isoquinoline (**5**) and a dark polymer



5

with a consequent decrease in the yield of **4a**. The structure of **5** was inferred from the following considerations: (1) IR showed a –CN; (2) NMR showed nine aromatic protons and a tenth at 9.29 ppm, characteristic of the proton in the 1 position of isoquinoline; and (3) its mass spectrum.

The reaction between phthalaldehyde and ammonia is strongly exothermic. The rate of ammonia addition had to be controlled carefully to maintain a low reaction temperature. Warming after the reaction had been completed did not affect the product composition, but at higher reaction temperatures greater amounts of polymer were formed at the expense of **4a** and **5**.

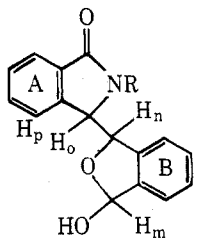
Reactions of excess aldehyde with primary amines in cold solutions (ether, acetone, benzene) produced **6** and N-substituted phthalimidines **4** as the major isolable products.

Elemental analyses of the products (**6**) from the primary amines showed that they were made up of 2 mol of aldehyde and 1 mol of amine with the loss of 1 mol of water. Mass spectra established their molecular weights and IR showed the presence of amide and hydroxyl groups, the latter of which was proved to be secondary by oxidation. In addition, the mass spectra indicated cleavage into two major fragments, each

Table I. The Effect of N Substituent on Proton Chemical Shifts (ppm) in 6

Substituent (R)	H_m	$\Delta\delta H_m$[a]	H_p	$\Delta\delta H_p$	H_n	$\Delta\delta H_n$	H_o	$\Delta\delta H_o$
-Me	5.86		6.60		6.06		5.11	
$-CHMe_2$	5.66	−0.20	6.31	−0.29	6.02	−0.04	5.15	+0.14
$-CMe_3$	5.13	−0.73	5.85	−0.75	6.08	+0.02	5.32	+0.21
-Ph	5.28	−0.58	6.58	−0.02	6.03	−0.03	5.78	+0.67
$-2,6\text{-}Me_2Ph$	5.63	−0.23	6.25	−0.35	5.63	−0.43	5.30	+0.19

[a] Referred to the Me compounds.



6a, R = Me
b, R = *i*-Pr
c, R = *n*-Bu
d, R = *t*-Bu
e, R = Ph
f, R = $2,6\text{-}Me_2Ph$

containing a phenyl group and one of which was identifiable as coming from a phthalimidine-like structure.

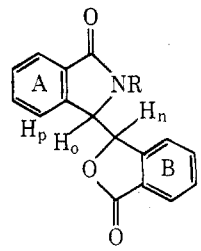
The NMR of the *tert*-butylamine product (**6d**) showed only seven protons in the aromatic region and a doublet at 5.85 ppm (J = 9 Hz), the coupling of which showed it to be aromatic and adjacent to a bridgehead. Furthermore, the aliphatic hydrogen of the secondary alcoholic group was found upfield (5.18 ppm) from the region usually associated with such a proton. ^{13}C NMR showed the *tert*-butyl group attached to the N atom.

Construction of the proposed structure (**6d**) from Catalin molecular models[10] showed crowding so severe that of the eight possible stereoisomers (four enantiomorphic pairs) only four would be expected to be formed. The NMR spectra indicate that one enantiomorphic pair is formed predominantly.

In the preferred conformation the aromatic hydrogen (H_p) is situated closely above the center of the aromatic ring B. This accounts for the upfield shift of the aromatic proton. Similarly, when H_m and H_n are trans, H_m is centered over the aromatic ring A, accounting for its comparable upfield shift. The *o*-methyl groups in **6f** prevent free rotation of the *N*-aryl group as indicated by models and by the nonequivalent absorptions of the two methyl groups. As a consequence H_n lies just above the *N*-aryl group and its absorption is shifted upfield to coincide with that of H_m.

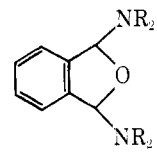
Further evidence supporting the proposed structure is found in the NMR spectra of the lower homologues of **6d.** The *N*-methyl derivative is much less crowded, allowing movement of H_m and H_p away from the phenyl rings, as compared to the *tert*-butyl derivative, and the chemical shifts are closer to the normal values for such protons. Chemical shifts of H_m and H_p in the isopropyl derivative **6b** are intermediate between those of the methyl and *tert*-butyl derivatives (Table I). Models show that the freedom of rotation between the two benzylic nuclei increases in the order *tert*-butyl < isopropyl < Me. The absorption due to H_n is relatively unaffected by the substituent on the N atom, but that due to H_o is shifted downfield as the bulkiness of the group on the N atom increases.

These compounds were readily oxidized in good yields to lactam lactones (**7**), for which the chemical shifts of H_n, H_o, and H_p are not appreciably different from those of the parent compounds.



7a, R = Me
b, R = *t*-Bu
c, R = Ph

Secondary amines reacted rapidly with equal moles of phthalaldehyde in Me_2SO to form intermediates whose structures were not determined. The reaction continued slowly, forming **8** and regenerating 0.5 mol of phthalaldehyde.

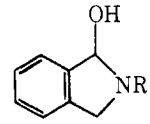


8a, R = Me
b, R = Et
c, R = $-(CH_2)_5-$
d, R = $-(CH_2)_2O(CH_2)_2-$

In the presence of excess amine the initial product underwent conversion to **8** quantitatively as inferred from NMR spectra. The structure of **8b** was established by NMR and mass spectrometry.

Discussion

The reactions between phthalaldehyde and ammonia or amines may be rationalized best by a 1-hydroxyisoindole intermediate (**9**) from transannular dehydration of the adducts (**3a–d**).[11] Under conditions of low temperature and high dilution, hydroxyisoindoles could rearrange to phthalimidines (**4**) by two 1,3-hydrogen shifts.

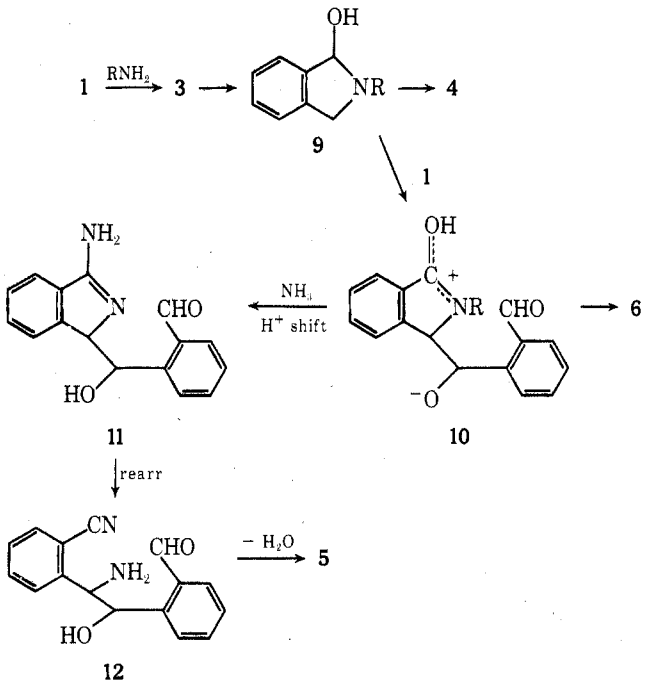


9a, R = H
b, R = alkyl, aryl

Higher concentrations and temperatures favor the formation of colored polymers. Isoindole is known to be highly reactive, readily forming dark tars under mild conditions.[12] Isoindole and its derivatives are most reactive in the 1 and 3 positions toward dienophiles.[13–17] The 1-phenyl derivative also resinifies readily, and it can be dimerized oxidatively through the 3 position by refluxing in benzene.[18]

The formation of cyanophenylisoquinoline (**5**) can be rationalized by rapid dehydration of **3a** as it is formed, producing the isoindole **9a** which, by polar addition to unreacted phthalaldehyde present in the early stages of the reaction, would produce **10a** (Scheme I). Subsequent attack on **10a** by

Scheme I



a, R = H
b, R = alkyl or aryl

ammonia (in excess as the addition continues) followed by a proton shift would form the amidine **11**.[19] The latter may tautomerize to the unstable iminoamide which opens to the isomeric benzonitrile **12**, and ring closure followed by dehydration would produce cyanophenylisoquinoline (**5**).

A similar sequence of reactions can explain the products **6** from primary amines via the similar intermediate **10b**. The reaction is amine limited so that the replacement of the -OH of **10b** would not occur. Since N substitution would prevent rearrangement to an amidine, cyclization via the alkoxy anion would be favored and **6** would be produced.

Experimental Section

Water Adduct of Phthalaldehyde (2). A water (or D_2O) slurry of phthalaldehyde was stirred for 2 days, during which time the aldehyde dissolved. The mixture was filtered and the filtrate was analyzed by NMR: NMR (D_2O) δ 6.14, 6.45 (s, s, 2, *cis*- and *trans*-OCHOH), 7.35 (s, 4, aromatic). The assignments of the absorptions for cis and trans isomers are based on those reported for the 1,3-dialkoxyphthalans and the polymer of phthalaldehyde.[20]

Ammonia Adduct of Phthalaldehyde (3a). A solution of 0.2 g of phthalaldehyde in 50 mL of anhydrous ether was cooled to 0 °C, and dry NH_3 was bubbled into the solution. A white solid formed immediately. The solution was centrifuged and the white precipitate was dried at −70 °C in vacuo: mass spectrum (70 eV) *m/e* 230, 134 (molecular ion minus H_2O), 133, 105, 77, 51, 50; after silation (*N,O*-bis(trimethylsilyl)trifluoroacetamide) 205 (molecular ion minus H_2O), 190, 147, 133, 116, 105, 104, 77, 75, 74, 73. This result suggests monosilation and loss of 1 mol of water.

Anal. Calcd for $C_8H_9NO_2$: C, 63.6; H, 6.0; N, 9.3. Found: C, 62.8; H, 5.8; N, 8.9.

The solid was very unstable, accounting for the poor elemental analysis and the trace material of mass 230 in the mass spectrum. Upon being warmed to room temperature, it darkened and formed a tarry polymer from which was extracted phthalimidine as the only identifiable product.

A solution of phthalaldehyde in Me_2SO (5%) was cooled to 18–20 °C and dry ammonia was bubbled into the solution. The solution contained **3a**: NMR (Me_2SO) δ 5.00, 5.36 (s, s, 2, *cis*- and *trans*-CHOH), 7.27 (s, 4, aromatic).

After standing for several hours at room temperature the initial product was converted quantitatively to phthalimidine (**4a**), identified by comparison of UV, NMR, and mass spectra to those of an authentic sample:[9] UV (CH_3CN) 220 (ϵ 1.09 × 10^4), 262 (ϵ 1.31 × 10^3), 268 (ϵ 1.55 × 10^3), 275 nm (ϵ 1.38 × 10^3); NMR (Me_2SO) δ 4.41 (s, 2, $-CH_2-$), 7.60 (m, 4, aromatic), 8.54 (s, 1, >NH); mass spectrum (70 eV) *m/e* 133 (molecular ion), 132, 105, 104, 77.

3-(2-Cyanophenyl)isoquinoline (5). A solution of phthalaldehyde in Me_2SO (20%) was cooled to 15 °C and dry ammonia was bubbled into the solution at a rate such that the temperature did not rise above 18 °C. After the reaction was complete, the yellow solution was allowed to stand overnight, during which time it darkened. The solution was added to ten times its volume of water and the solid was filtered. The filtrate contained mainly phthalimidine and traces of the cyanophenylisoquinoline.

The dried residue was extracted in a Soxhlet apparatus with hexane. The hexane solution rapidly assumed a blue fluorescence from the dissolved cyanophenylisoquinoline. Removal of solvent gave crude **5** in 30% yield. Repeated crystallization from hexane gave pale yellow silky needles: mp 104–105 °C; UV max (CH_3CN) 222 (ϵ 4.42 × 10^4), 295 (ϵ 9.52 × 10^3), 320 nm (ϵ 4.4 × 10^3); IR (KBr) 2220 cm^{-1} (CN); NMR δ 8.00 (m, 9, aromatic), 9.29 (s, 1, H_1 of isoquinoline); mass spectrum (70 eV) *m/e* (major peaks italicized) *230* (molecular ion), *229*, 203, 202, 201, 176, 175, 102, 101, 77, 76, 75. Elemental analyses consistently were low for no apparent reason.

Anal. Calcd for $C_{16}H_{10}N_2$: C, 83.5; H, 4.4; N, 12.15. Found: C, 82.3; H, 4.1; N, 11.9.

Reactions Involving Excess Primary Amine. (1) Methylamine. Dry CH_3NH_2 was bubbled into a Me_2SO solution of phthalaldehyde (10%) maintained at a temperature below 20 °C. The solution contained **3b**: NMR (Me_2SO) δ 5.08, 5.47 (s, s, 2, *cis*- and *trans*-CHOH), 7.37 (m, 4, aromatic).

After a few hours these absorptions disappeared and the spectrum became identical with that of *N*-methylphthalimidine (**4b**):[21] NMR (Me_2SO) δ 4.37 (s, 2, $-CH_2-$), 7.50, 8.1 (m, 4, aromatic).

(2) Aniline. To a stirred solution of 4.0 g (0.03 mol) of phthalaldehyde in 75 mL of ether was added 3.0 g (0.032 mol) of aniline in 75 mL of ether, whereupon **3c** precipitated at once as a colorless solid, 5.2 g (77%). It was filtered and dried in vacuo: IR (KBr) 3280 (OH), 1680 (C=O), 1600, 1500 cm^{-1}; NMR (Me_2SO) δ 5.51, 5.93 (d, d, 4, AB pair, J = 18 Hz, -CHOH), 7.14 (m, 4, aromatic), 7.40 (s, 5, aromatic); NMR (Me_2SO–D_2O) δ 6.03 (s, 2, -OCHNPh–), 7.22 (m, 4, aromatic), 7.49 (s, 5, aromatic); mass spectrum (70 eV) *m/e* 209 (molecular ion minus H_2O), 208, 181, 160, minor components (a) 284, 283, (b) 298, 297, (c) 400, 399, 371.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.7; N, 6.2. Found: C, 73.6; H, 5.7; N, 6.1.

The compound **3d** decomposed while the IR spectrum was being recorded; the hydroxyl absorption disappeared and the carbonyl absorption was enhanced.

From the filtrate was isolated a small amount of a yellow solid, which consisted of a mixture of 2-phenylphthalimidine[22] and 2-phenyl-1-phenyliminoisoindoline.[23] Recrystallization from benzene produced colorless prisms (0.25 g) of impure 2-phenylphthalimidine (**4c**), mp 157–160 °C, identified by IR, NMR, and mass spectra in comparison to an authentic sample.

Reactions Involving Excess Phthalaldehyde. (1) Methylamine. To a stirred solution of 12.0 g (0.09 mol) of phthalaldehyde in 200 mL of acetone was added 4.5 g (0.06 mol) of 40% aqueous methylamine in 100 mL of acetone. The solution turned pale yellow immediately and then darkened gradually to a reddish color as the product crystallized from the solution. The mixture was chilled in the refrigerator and filtered to give 6 g (35%) of **6a**. Recrystallization twice from acetone or methanol gave colorless needles: mp 220–222 °C dec; UV max (CH_3CN) 228 (ϵ 892), 248 (ϵ 506), 269 (ϵ 333), 276 nm (ϵ 213); IR 3380 (OH), 1680 cm^{-1} (-C(=O)N–); NMR (Me_2SO) δ 3.05, 3.07 (s, s, 3, >NCH_3), 5.11 (m, 1, $-OCH_nN-$), 5.83, 5.90 (d, d, 1, J = 2 Hz, $-O-CH_mOH$), 6.06 (m, 1, $-OCH_nO-$), 6.60 (d, 1, J = 9 Hz, H_p), 6.82 (d, 1, J = 8 Hz, -OH), 7.4 (m, 7, aromatic); NMR (Me_2SO, silated) δ 3.03, 3.05 (s, 3, >NCH_3), 5.10 (m, 1, $-OCH_nN-$), 6.07 (m, 2, -OCHOSiMe_3, $-OCH_nO-$), 7.3 (m, 7, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 282 (molecular ion), 264, 247, 165, *147*, *146*, 135, 118, 117, 91, 77; after silation (*N,O*-bis(trimethylsilyl)trifluoroacetamide), 425 (molecular ion), 338, 337, 322, *219*, *207*, *146*, *118*, *73*.

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.6; H, 5.4; N, 5.0. Found: C, 72.3; H, 5.6; N, 4.9.

The NMR spectrum shows two different -NMe absorptions indicative of at least two isomeric compounds, one of which is present to a minor extent.

(2) Isopropylamine. To a stirred solution of 5.0 g (0.037 mol) of phthalaldehyde in 75 mL of dry ether was added 1.24 g (0.021 mol) of isopropylamine in 75 mL of dry ether. The product **6b** crystallized from the solution as fine colorless prisms: mp 186–188 °C dec; UV max (CH_3CN) 229 (ϵ 820), 248 (ϵ 470), 268 (ϵ 341), 276 nm (ϵ 222); IR (KBr) 3400 (OH), 1680 cm^{-1} (-C(=O)N); NMR (Me_2SO) δ 1.38 (d, 6, J =

8 Hz, -CH(CH_3)$_2$), 4.20 (septet, 1, J = 8 Hz, -C**H**(CH_3)$_2$), 5.15 (m, 1, -OCH_oN<), 5.62, 5.70 (d, d, 1, J = 4 Hz, -O**C**H_mOH), 6.02 (m, 1, -OCH_nO-), 6.31 (d, 1, J = 8 Hz, H_p), 6.78 (d, 1, J = 8 Hz, -OC**H**O**H**), 7.5 (m, 7 aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 310 (molecular ion), 309, *175*, 174, 135, 133, 132, 104, 77.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5. Found: C, 73.8; H, 6.4; N, 4.6.

(3) *n*-Butylamine. A reaction similar to that with isopropylamine was run with *n*-butylamine. The product (**6c**) crystallized from the solution as fine colorless prisms: mp 177–179 °C dec; mass spectrum (70 eV) *m/e* (major peaks italicized) 324 (molecular ion), 305, *189*, *147*, *146*, 135, *132*, 119, 104, 90, 77.

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.3; H, 6.5; N, 4.3. Found: C, 74.0; H, 6.8; N, 4.3.

(4) *tert*-Butylamine. The reaction was run as that with *n*-butylamine. The product **6d**, 3.0 g (50%), crystallized from the solution as fine colorless prisms: mp 218–220 °C dec; UV max (CH_3CN) 229 (ε 810), 253 (ε 453), 269 (ε 364), 276 nm (ε 225); IR (KBr) 3380 (OH), 1680 cm^{-1} (-C(=O)N-); NMR (Me_2SO) δ 1.60, 1.64 (s, s, 9, >NC(CH_3)$_3$), 5.10 5.18 (d, d, 1, J = 2 Hz, -O**C**H_mOH), 5.32 (m, 1, -O**C**H_oN<), 5.85 (d, 1, J = 9 Hz, H_p), 6.08 (m, 1, -OCH_nO-), 6.83 (d, 1, J = 10 Hz, OH), 7.4 (m, 7, aromatic); NMR (Me_2SO–D_2O) δ 1.62, 1.64 (s, s, 9, >NC(CH_3)$_3$), 5.15 (d, 1, J = 2 Hz, -O**C**H_mOH), 5.32 (m, 1, -OCH_oN<), 5.79 (d, 1, J = 9 Hz, H_p), 6.08 (m, 1, -CH_nO-), 7.4 (m, 7, aromatic); ^{13}C NMR (Me_2SO) δ 28.2 (-C(CH_3)$_3$), 54.3 (>N**C**Me_3), 63.9 (-CH-), 81.7 (-CH-), 100.7 (-CH-), 121.8, 122.9, 127.7, 128.8, 129.5, 135.1, 139.1, 140.9, 141.0 (12 aromatic), 168.0 (C=O); mass spectrum (70 eV) *m/e* (major peaks italicized) 324 (molecular ion), 305, *189*, 144, *135*, *133*, *132*, 105, 104, *77*; after silation (*N*,*O*-bis(trimethylsilyl)trifluoroacetamide), 467 (molecular ion), 395, 394, 380, 324, *261*, *207*, 188, 132, 130, 77, 75, 73.

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.3; H, 6.5; N, 4.3. Found: C, 74.0; H, 6.7; N, 4.2.

The NMR spectrum shows two *tert*-butyl absorptions indicative of at least two isomers being present, one of which is in a relatively small proportion.

(5) Aniline. To a stirred solution of 5.0 g (0.037 mol) of phthalaldehyde in 75 mL of acetone was added dropwise 2.3 g (0.025 mol) of aniline in 75 mL of acetone. The solution gradually turned yellow and then deep red. The solution was heated and stirred at the boiling point for 1 h and then evaporated to dryness. To the red tar was added 25 mL of benzene and the slurry was filtered to obtain 2.5 g (39%) of crude product, which crystallized from acetone as colorless prisms (**6e**): mp 196–198 °C dec; IR (KBr) 3280 (OH), 1670 cm^{-1} (-C(=O)-N-); NMR (Me_2SO) δ 5.28 (m, 1, -OCH_oN<), 5.78 (m, 1, -O**C**H_mOH), 6.03 (d, 1, J = 2 Hz, -OCH_nO-), 6.58 (d, 1, J = 9 Hz, H_p), 6.65 (m, 1, -OH), 7.5 (m, 12, aromatic); NMR (Me_2SO–D_2O) δ 5.28 (d, 1, J = 2 Hz, -OCH_mOH), 5.78 (m, 1, -OCH_oN<), 6.02 (d, 1, J = 2 Hz, -OCH_nO-), 6.58 (d, 1, J = 9 Hz, H_p), 7.5 (m, 12, aromatic); NMR (pyridine) δ 5.86, 5.95, 6.05 (m, 3, -OCHO-), 6.70 (d, 1, J = 9 Hz, aromatic), 7.35 (m, 9, aromatic), 7.98, 8.06 (m, 3, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 341 (molecular ion), *208*, 180, 179, 152, 133, 77.

Anal. Calcd for $C_{22}H_{17}NO_3$: C, 77.0; H, 5.0; N, 4.1. Found: C, 76.9; H, 5.2; N, 4.0.

The filtrate contained 2-phenylphthalimidine.

(6) 2,6-Dimethylaniline. The reaction was run as that with isopropylamine. The product, 0.6 g (8.7%), crystallized slowly from the solution as colorless needles (**6f**), which were recrystallized from ethanol: mp 248–250 °C dec, with prior discoloration at 235–240 °C; IR (KBr) 3300 (OH), 1675 cm^{-1} (C=O); NMR ($CDCl_3$–Me_2SO) δ 2.20 (s, 1, -CH_3), 2.25, 2.30 (s, s, 6, -CH_3), 5.30 (s, 1, -OCH_oN<), 5.64 (m, 2, -OCH_nO-, -O**C**H_mOH), 6.25 (d, 1, J = 9 Hz, H_p), 6.65 (d, 1, J = 8 Hz, OH), 7.20 (s, 3, aromatic), 7.35–8.00 (m, 7, aromatic); NMR ($CDCl_3$–Me_2SO–D_2O) δ 2.20 (s, 1, -CH_3), 2.25, 2.30 (s, s, 6, -CH_3), 5.29 (m, 1, -OCH_oN<), 5.64 (m, 2, -OCH_nO-, -O**C**H_mOH), 6.25 (d, 1, J = 9 Hz, H_p), 7.26 (s, 3, aromatic), 7.30–8.00 (m, 7, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 372 (molecular ion), 354, *237*, 236, 220, 218, 135, 132, 106, 105.

Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.6; H, 5.7; N, 3.8. Found: C, 77.4; H, 5.6; N, 3.6.

From the filtrate was isolated 4.0 g of 2-(2,6-dimethylphenyl)-phthalimidine (**4d**), which crystallized from ligroine in colorless prisms: mp 139–141 °C; IR 1675 cm^{-1} (C=O); NMR (Me_2SO) 2.2 (s, 6, -CH_3), 4.73 (s, 2, -CH_2-), 7.23 (s, 3, aromatic), 7.5–8.0 (m, 4, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) *237* (molecular ion), 222, 220, 165, *132*, 106.

Anal. Calcd for $C_{16}H_{15}NO$; C, 81.0; H, 6.3; N, 5.9. Found: C, 81.0; H, 6.3; N, 5.9.

Oxidation of Dimeric Products. (1) Oxidation of 6a. To a stirred suspension of 2.0 g (0.007 mol) of **6a** in 50 mL of pyridine was added 2.0 g (0.02 mol) of CrO_3 in small portions over 15 min. Stirring was continued for 48 h. The mixture was poured into water and extracted with ether. Removal of the ether and crystallization of the colorless residue from methanol gave 1.6 g (80%) of colorless prisms of **7a**: mp 212–215 °C dec; UV (CH_3CN) 222 (ε 1.81 × 10^4), 228 (ε 1.47 × 10^4), 268 (ε 351), 275 nm (ε 314); IR (KBr) 1680 (-C(=O)N-), 1760 cm^{-1} (-C(=O)O); NMR ($CDCl_3$, Me_2SO) δ 3.12 (m, 3, >NCH_3), 5.28 (d, 1, J = 3 Hz, -OCH_oN<), 6.28 (d, 1, J = 3 Hz, -OCH_nO-), 6.78 (m, 1), 6.96 (m, 1, aromatic), 7.6 (m, 6, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 279 (molecular ion), 165, 162, *146*, 133, 118, 117, 105, 91, 77, 42.

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.7; N, 5.0. Found: C, 72.8; H, 5.1; N, 4.9.

(2) Oxidation of 6d. The oxidation was carried out as described for the methyl derivative. The product (**7b**) crystallized from methanol as colorless prisms (70%): mp 236–248 °C dec; IR (KBr) 1680 (-C(=O)N-), 1760 cm^{-1} (-C(=O)O); NMR (Me_2SO) δ 1.58, 1.62 (s, 9, -C(CH_3)$_3$), 5.65 (d, 1, J = 2 Hz, -OCH_oN<), 5.70 (d, 1, J = 9 Hz, H_p), 6.38 (d, 1, J = 2 Hz, -OCH_nO-), 6.95–8.0 (m, 7, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 322 (molecular ion), 321, 306, 266, 248, *188*, *132*, 104, 77, 57.

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.8; H, 5.9; N, 4.4. Found: C, 75.2; H, 6.1; N, 4.5.

(3) Oxidation of 6e. The oxidation was carried out as described for the methyl derivative. The product (**7c**) crystallized from methanol as colorless prisms (83%): mp 227–229 °C; IR (KBr) 1680 (-C(=O)-N-), 1760 cm^{-1} (-C(=O)O); NMR (Me_2SO) δ 6.09 (d, 1, J = 2 Hz, -OCH_oN<), 6.39 (d, 1, J = 2 Hz, -OCH_nO-), 6.55 (d, 1, J = 9 Hz, H_p), 7.6 (m, 12, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 341 (molecular ion), *208*, 180, 179, 152, 133, 77.

Anal. Calcd for $C_{22}H_{15}NO_3$: C, 77.4; H, 4.4; N, 4.1. Found: C, 77.2; H, 4.5; N, 3.8.

Reactions with Secondary Amines. The amine (0.2 g) was added to 0.41 g of a 15% solution of phthalaldehyde in dimethyl sulfoxide, and the solution was allowed to stand at room temperature. The reaction was followed by NMR.

Immediately after addition of the amine, absorptions were observed in the regions 5.75–5.90 (s, 1), 6.02–6.20 (d, 1, J = 4 Hz), 6.23–6.29 (s, 1), 6.33–6.38 ppm (d, 1, J = 4 Hz). Upon being warmed to 45 °C or standing at room temperature for 2 weeks, the product was converted to the isobenzofurans **8** as show by NMR. Absorptions of the products contained two singlets associated with the *cis*- and *trans*-O**C**HNR_2 as follows: **8a** (5.67, 5.92); **8b** (5.77, 6.03); **8c** (5.64, 5.84); **8d** (5.70, 5.90).

A 10% solution of phthalaldehyde in diethylamine was warmed to the boiling point. Removal of the excess amine and distillation of the residue produced **8b** as a colorless oil (80%): bp 58–59 °C (15 μm); NMR (neat) δ 1.0 (m, 12, -CH_2CH_3), 2.65 (m, 8, -CH_2CH_3), 5.82, 5.96 (s, s, 2, *cis*- and *trans*-O**C**HNEt_2), 7.23 (s, 4, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 262 (molecular ion), 233, 191, *190*, 162, *160*, 134, 132, 199, 118, 116, 91, 77.

Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.2; H, 10.0; N, 10.7. Found: C, 73.2; H, 10.0; N, 10.5

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Registry No.—**1**, 643-79-8; *cis*-**2**, 63883-89-6; *trans*-**2**, 63883-90-9; *cis*-**3a**, 63883-91-0; *trans*-**3a**, 63883-92-1; *cis*-**3b**, 63883-93-2; *trans*-**3b**, 63883-94-3; **3c**, 63883-95-4; **4a**, 480-91-1; **4b**, 5342-91-6; **4c**, 5388-42-1; **4d**, 63883-96-5; **5**, 63883-97-6; **6a**, 63883-98-7; **6b**, 63883-99-8; **6c**, 63884-00-4; **6d**, 63884-01-5; **6e**, 63884-02-6; **6f**, 63884-03-7; **7a**, 63904-77-8; **7b**, 63884-04-8; **7c**, 63884-05-9; *cis*-**8a**, 63884-06-0; *trans*-**8a**, 63884-07-1; *cis*-**8b**, 63884-08-2; *trans*-**8b**, 63884-09-3; *cis*-**8c**, 63884-10-6; *trans*-**8c**, 63884-11-7; *cis*-**8d**, 63884-12-8; *trans*-**8d**, 63884-13-9; water, 7732-18-5; ammonia, 7664-41-7; methylamine, 74-89-5; aniline, 62-53-3; isopropylamine, 75-31-0; *n*-butylamine, 109-73-9; *tert*-butylamine, 75-64-9; 2,6-dimethylaniline, 87-62-7; diethylamine, 109-89-7; dimethylamine, 124-40-3; piperidine, 110-89-4; morpholine, 110-91-8.

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Isolation of Potent New Antileukemic Trichothecenes from *Baccharis megapotamica*[1,2]

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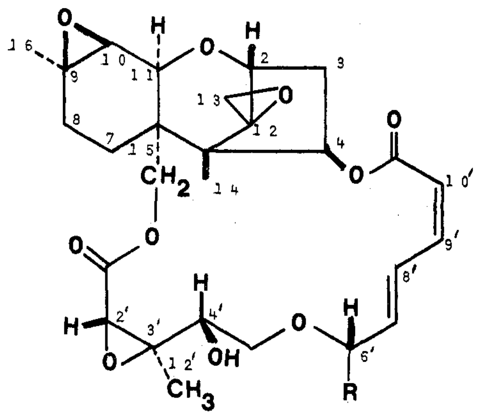
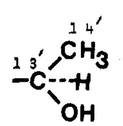
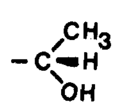
The isolation and structural elucidation of the new potent antileukemic trichothecenes baccharin (1), baccharinol (2), isobaccharinol (3), and isobaccharin (4) are reported. Baccharinol (2) and isobaccharinol (3) were shown to be esters of 8β-hydroxyverrucarol (9) by hydrolysis to 9 and the dimethyl esters 5 and 11. Hydrolysis of baccharin (1) and isobaccharin (4) gave 6 and esters 5 and 11. Conversion of 2 and 3 to the common intermediate 13 demonstrated that 4 and 3 were the C-13′ epimers of 1 and 2, respectively.

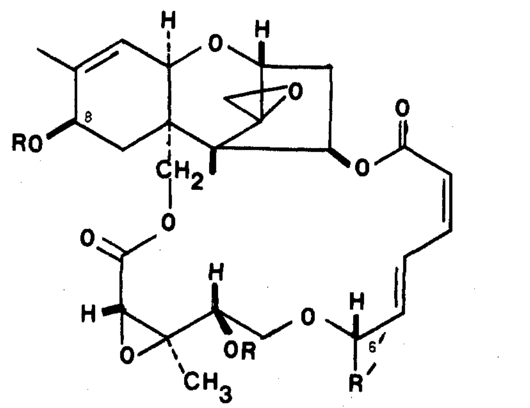
In the course of a continuing search for tumor inhibitors of plant origin, an alcoholic extract of *Baccharis megapotamica* Spreng (Asteraceae)[4] was found to show significant activity in vivo against P-388 leukemia in mice (PS)[5] and in vitro against cells derived from human carcinoma of the nasopharynx (KB). A preliminary communication[6] described the structural elucidation of the potent antileukemic trichothecene triepoxide baccharin (1). It is the purpose of this paper to present in detail the isolation and structural elucidation of baccharin (1), as well as the new potent antileukemic principles baccharinol (2), isobaccharinol (3), and isobaccharin (4).[7]

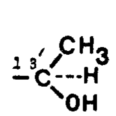
Fractionation of the alcohol extract, guided by a combination of P-388 in vivo assay in mice and KB testing in vitro, revealed that the inhibitory activity was concentrated, suc-

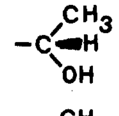


1, R = 

4, R = 



2, R = H ; R′ = 

3, R = H ; R′ = 

7, R = Ac ; R′ =