When the amount of manganese dioxide employed for the oxidation of aniline was decreased from 0.4 to 0.3 to 0.2 mole, the yield of azobenzene decreased from 91 to 75 to 48%. When the temperature was decreased from 111 to 81 to 52°, by changing the solvent, the corresponding yields of azobenzene were 85, 91, and 76%.

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Ring Closure of Ylidenemalononitriles. III.[1] Formation of Six-Membered Rings and Related Chemistry[2]

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Several γ-aryl ylidenemalononitriles, including that of a phenylacetaldehyde derivative, were cyclized in concentrated sulfuric or polyphosphoric acid to 1-naphthylamine derivatives. Surprisingly, ylidenemalononitriles derived from α-acetonaphthalene did not form six-membered rings *via* cyclization to the 8-position. Hydration to the *trans*-cyanoamide was the principal reaction in these cases. The ring closure was shown to proceed by attack of a protonated nitrile group, rather than an amido group, on the aromatic ring, by cyclizing *cis*-2-cyano-3-methyl-4-phenyl-2-butenamide, a reaction which failed for the *trans* isomer. The configuration of the isomers was established by n.m.r. studies. The ultraviolet absorption spectra of the hindered and unhindered 2-cyano- and 2-carboxamido-1-naphthylamines produced by these cyclizations are discussed.

Substituted indenones and indanones can be produced by strong acid treatment of the appropriate ylidenemalononitriles.[1,4] From the ring closure of these dinitriles, compounds containing newly formed five-membered rings were obtained. The study of this facile ring closure has now been extended to ylidenemalononitriles leading to six-membered rings.

Cyclizations of aromatic derivatives of nitriles to form six-membered cyclic ketones and aromatic amines are well known. Atkinson and Thorpe[5] prepared a series of 1,3-diaminonaphthalene derivatives by ring closing various derivatives of ethyl β-imino-α-phenylbutyrate in sulfuric acid. *o*-Biphenylacetonitrile and its derivatives have been converted to phenanthrylamines or phenanthrones by an intramolecular cyclization in sulfuric acid.[6] Howell and Taylor[7] prepared 1,2,3,4-tetrahydrofluoren-1-one from γ-3-indenylbutyronitrile in the presence of anhydrous zinc chloride and hydrogen chloride. Several other papers[8] report cyclizations involving nitrile groups to form six-membered heterocyclic compounds. The conversion of γ-(1-cyclohexenyl)butyronitrile to Δ^9-1-octalone in polyphosphoric acid[9] showed that ring closure of a nitrile can also occur by electrophilic attack on an olefinic double bond.

Only two reports have been found describing the cyclization of an ylidenemalononitrile to form a six-membered ring. Dufraisse and Etienne[10] accomplished the bicyclization of 1,3-diphenylisopropylidenemalononitrile to 11,12-diaminonaphthacene in a phosphoric acid–sulfuric acid–phosphorus pentoxide mixture. Jaeger[11] describes the ring closure of 2-(cyclohexylidene)cyclohexylidenemalononitrile to 10-amino-9-cyano-1,2,3,4,5,6,7,8-octahydrophenanthrene in sulfuric acid.

As shown by earlier results,[4] good yields of α-carboxamido-α,β-unsaturated ketones were obtained from the ring closure of certain α-cyano-β-substituted cinnamonitriles. In most instances, the second nitrile was hydrated during cyclization. It was of interest to investigate cyclizations of ylidenemalononitriles which could lead to six-membered cyclic compounds having the partial structure **1**, especially since this structure is present in certain antibiotics.

It was found that treatment of several ylidenemalononitriles (**2**) with sulfuric acid gave good yields of newly formed six-membered rings. The ring closure of ylidenemalononitrile **2a** to 2-cyano-3,4,4-trimethyl-1-keto-1,4-dihydronaphthalene (**4**) has already been reported.[4b] Ylidenemalononitriles (**2**), with R^1 = H, were prepared (Table I) and were all ring closed to derivatives of 1-naphthylamine (Table II).

A good yield of 2-cyano-3-methyl-1-naphthylamine (**3a**, Z = CN) was obtained when phenylisopropylidenemalononitrile (**2b**) was allowed to stand in concentrated sulfuric acid at room temperature for 1 hr. It was interesting to note that the amine was isolated from the acid solution after the reaction mixture was poured over ice. No further product was isolated when the mother liquor was made basic. The second nitrile group resisted hydration similar to that of **4** mentioned above. However, when the sulfuric acid solution was heated for 1 hr. at 90°, only the hydrated product **3a**

(1) Previous paper II: E. Campaigne, R. Subramanya, and D. R. Maulding, *J. Org. Chem.*, **28**, 623 (1963).

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(3) Taken in part from the (a) Ph.D. thesis of D. Maulding, June, 1962, Bristol Predoctoral Fellow, 1960–1962; (b) Ph.D. thesis to be submitted by W. Roelofs, National Institute of Health Predoctoral Fellow, 1962–1964.

(4) (a) E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum, and D. R. Maulding, *J. Org. Chem.*, **27**, 4428 (1962); (b) E. Campaigne and D. R. Maulding, *ibid.*, **28**, 1391 (1963).

(5) E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **89**, 1906 (1906).

(6) C. K. Bradsher, D. J. Beavers, and E. D. Little, *J. Am. Chem. Soc.*, **76**, 948 (1954); **78**, 2153 (1956).

(7) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 3011 (1957).

(8) (a) A. Schaarschmidt, *Ann.*, **409**, 59 (1915); (b) J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, **27**, 1659 (1962); (c) C. R. Hauser and J. G. Murray, *J. Am. Chem. Soc.*, **77**, 2851 (1955); (d) M. Lamant and M. Le Moine, *Bull. soc. chim. France*, 2150 (1962); (e) W. Baker, A. Pollard, and R. Robinson, *J. Chem. Soc.*, 1468 (1929).

(9) R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960).

(10) C. Dufraisse and A. Etienne, *Compt. rend.*, **239**, 1744 (1954); **240**, 265 (1955).

(11) H. Jaeger, *Chem. Ber.*, **95**, 242 (1962).

TABLE I

PREPARATION AND PROPERTIES OF YLIDENEMALONONITRILES

Compound	Reaction time, hr.	Yield, %	B.p. (mm.) or m.p., °C.	$n^{24}D$	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
2b	8	78	120 (0.4)	1.5518	$C_{12}H_{10}N_2$			15.38			15.51
2c	12	74	67–68[a]		$C_{12}H_{14}N_2$						
2d	5	75	93–94 (0.01)	1.5442	$C_{12}H_{10}N_2$	79.09	5.53	15.38	78.80	5.57	15.53
2e	15	70	142–143 (0.05)	1.5446	$C_{16}H_{18}N_2O$	75.59	7.13	11.02	75.46	7.21	11.26
5a	3	90	168–169[b]		$C_{14}H_8N_2$						
5b	24	40	73–74		$C_{15}H_{10}N_2$	82.52	4.62	12.84	82.68	4.50	13.24

[a] J. G. Murphy [*J. Org. Chem.*, **26**, 3104 (1961)] reported m.p. 67–68° and a 97% yield. [b] H. G. Sturz and C. R. Noller [*J. Am. Chem. Soc.*, **71**, 2949 (1949)] report m.p. 170–171.5°; B. B. Corson and R. W. Stoughton [*ibid.*, **50**, 2825 (1928)] report m.p. 173.5–174.5°.

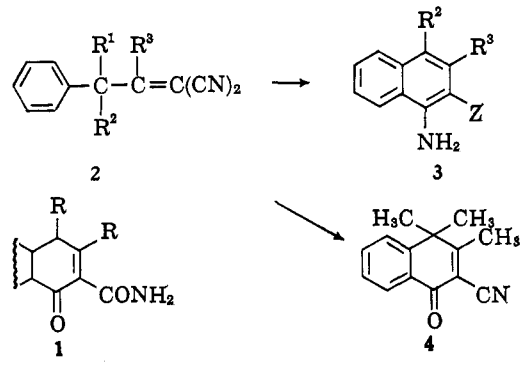
TABLE II

RING CLOSURE OF YLIDENEMALONONITRILES TO NAPHTHYLAMINE DERIVATIVES

Reactant	Reaction time, hr.[a]	Temp., °C.	% yield of **3**, Z = CN	% yield of **3**, Z = $CONH_2$
2b	1	25[b]	73	0
	1	90	0	72
2c	6	25	80	0
	0.33	90	22	1
	4[c]	90	0	62
2d	1	5	63	0
	1	25	57	28
	0.125	90	0	44,[d] 45
2e	0.33[c]	120	10	0

[a] In sulfuric acid unless otherwise stated. [b] Room temperature, approximately 25°. [c] In polyphosphoric acid. [d] Bisulfate salt.

($Z = CONH_2$) was isolated. In this case, the product precipitated only after basification of the dilute acidic solution.



2a, $R^1 = R^2 = R^3 = CH_3$
b, $R^1 = R^2 = H$; $R^3 = CH_3$
c, $R^1 = H$; R^2–R^3 = $—CH_2CH_2CH_2CH_2—$
d, $R^1 = R^3 = H$; $R^2 = CH_3$
e, *p*-OCH_3, $R^1 = H$; $R^2 = R^3 = C_2H_5$

3a, $R^2 = H$; $R^3 = CH_3$
b, R^2–R^3 = $—CH_2CH_2CH_2CH_2—$
c, $R^2 = CH_3$; $R^3 = H$
d, 7-OCH_3, $R^2 = R^3 = C_2H_5$; Z = CN

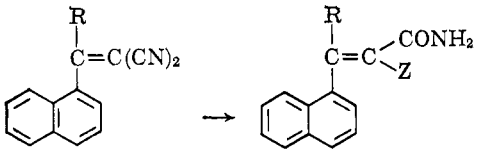
Cyclization of 2-phenylcyclohexylidenemalononitrile (**2c**) in concentrated sulfuric acid at room temperature gave 9-amino-10-cyano-1,2,3,4-tetrahydrophenanthrene (**3b**, Z = CN) as the sole product. Again this cyano derivative was isolated from the dilute acidic solution. Heating the reaction mixture on the steam bath for several hours gave the cyano derivative as the major product, but basification of the mother liquor yielded a small amount of the hydrated product **3b** ($Z = CONH_2$). Reaction in polyphosphoric acid on a steam bath for 4 hr. afforded the hydrated compound as the only product.

In the formation of five-membered rings[4] it was found that a bulky group on the α-position of the ylidenemalononitrile was necessary for ring closure. It was suggested that this group provided distortion of the ring-deactivating conjugated resonance system between the protonated nitrile and the aromatic ring, thus facilitating electrophilic attack by the $-C^+=NH$ group. In the present system, the protonated nitrile is not conjugated with the aromatic ring and, therefore, ring closure should be feasible with malononitrile adducts of phenylacetaldehyde derivatives containing only hydrogen on the α-position. The condensation of phenylacetaldehyde with malononitrile could not be effected due to side reactions involving the highly reactive methylene group of the aldehyde. The condensation with malononitrile was successful when one of the methylene hydrogens of the aldehyde was replaced by a methyl group, giving the adduct **2d**. The cyclization of **2d** is the first described for an aldehyde–malononitrile adduct. Treatment with sulfuric acid at 5° gave only 2-cyano-4-methyl-1-naphthylamine (**3c**, Z = CN), but, at room temperature, a mixture of the above cyano derivative and the hydrated product **3c** ($Z = CONH_2$) was obtained. Again the cyano derivative was isolated from the acidic solution and the hydrated product after basifying. Treatment in sulfuric acid at 90° followed by dilution with water caused the bisulfate salt of the hydrated product **3c** ($Z = CONH_2$) to precipitate from the acidic solution, and some free hydrated product was obtained on basification of the mother liquor. The bisulfate salt was readily converted to **3c** by stirring in an alkaline solution.

Ylidenemalononitrile **2e**, in which a methoxy group on the aromatic ring is so positioned that ring closure will occur at the *meta* position rather than the more active *ortho* or *para* positions, when treated with sulfuric acid, yielded a black tar when the reaction mixture was poured over ice, which could not be crystallized from organic solvents nor purified by column chromatography. Cyclization in polyphosphoric acid yielded a red solid, which proved to be the cyanoamine **3d**.

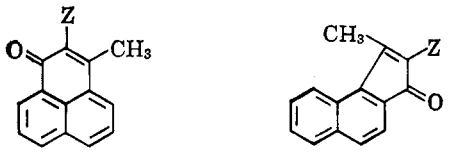
An attempt to extend the ring-closure reaction to ylidenemalononitriles of α-naphthyl derivatives was not successful. α-Naphthylmethylidenemalononitrile (**5a**) did not cyclize to form either a five- or six-membered ring when heated in concentrated sulfuric acid, but instead was hydrated to the cyanoamide **6a**. This is analogous to the results of strong acid treatment of benzylidenemalononitrile.[4a] In this case, ring closure might have occurred at the 8-position, forming a new

six-membered ring. The substitution of a methyl group for R on compound **5** did not enhance ring closure to the 8-position to form the six-membered ring compound **7**. Instead, treatment of compound **5b** with concentrated sulfuric acid produced a small amount of



5a, R = H
b, R = CH_3

6a, R = H; Z = CN
b, R = CH_3; Z = CN
c, R = CH_3; Z = $CONH_2$



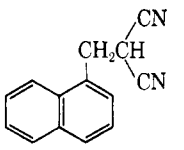
7a, Z = CN
b, Z = $CONH_2$

8a, Z = CN
b, Z = $CONH_2$

ring-closed product which appeared to be a mixture of **8a** and **b**. The products were separated by preparative thin layer chromatography (t.l.c.), but could not be purified by recrystallization. A small amount of pure red crystals was obtained by sublimation and assigned the structure **8a**. The analysis and the downfield shift of the methyl group resonance in the n.m.r. spectra to 2.74 p.p.m. (from tetramethylsilane) are consistent with either structure **7a** or **8a**. The carbonyl absorption, however, at 1710 cm.$^{-1}$ corresponds to that of a five-membered ring ketone. The compound isolated by t.l.c. and assigned structure **8b** also had carbonyl absorption corresponding to a five-membered ring ketone at 1695 cm.$^{-1}$. The carbonyl absorption of compounds analogous to the six-membered ring ketone of structure **7** has been reported to be in the range of 1632–1637 cm.$^{-1}$.[12]

Only hydration occurred on treating adduct **5b** in polyphosphoric acid, giving the diamide **6c** on prolonged heating, and the cyanoamide **6b** under milder conditions. The cyanoamide **6b** was also obtained when **5b** was treated with concentrated sulfuric acid in dimethylformamide. Only one isomeric form of the cyanoamides **6a** and **6b** was obtained in the above reactions as evidenced by movement as a single spot on thin layer chromatography plates. Structure **6**, with carboxamide *trans* to naphthyl, represents the least hindered configuration and, in the case of **6b**, was supported by n.m.r. data. The methyl group resonance of **6b** is shifted 0.15 p.p.m. downfield from that of **5b**, (δ 2.66), analogous to data from compound **15a**, also possessing carboxamide *cis* to methyl (see later discussion). The n.m.r. spectrum of **6a** could not be obtained because of low solubility.

It was thought that the ring closure might be effected if the double bond were reduced and resonance between the naphthalene ring and cyano groups eliminated. The reduction was accomplished quite smoothly by hydrogenation of **5a** over platinum oxide. The reduced adduct **9** gave only water-soluble products, probably the



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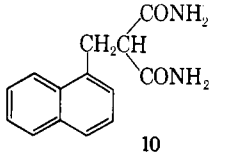

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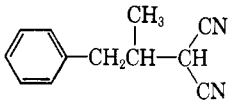

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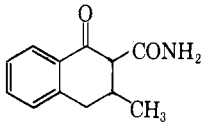

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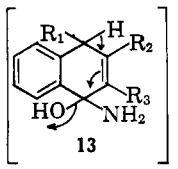
result of sulfonation, when treated with concentrated sulfuric acid, but formed the hydrated diamine **10** when treated with polyphosphoric acid. However, a six-membered ring was readily formed when the reduced adduct **11** was cyclized in concentrated sulfuric acid, forming the α-tetralone derivative **12**.

In discussing the mechanism of the ring closure of ylidenemalononitriles to six-membered rings, two possibilities must be considered. One possible mechanism involves the hydration of a cyano group and ring closure of the resulting amide.[8c] While by this mechanism one would expect naphthol as a result of ammonia elimination (apparent $k_{NH_3^+} >> k_{OH}$),[13a] still elimination of water from **13** could lead to the aromatic amine. The other mechanism would require ring closure by



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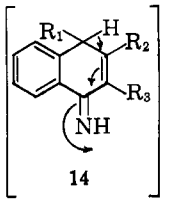

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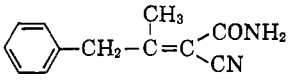
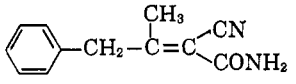
attack of protonated nitrile on the aromatic ring to give an imine intermediate **14**. Evidence supporting the latter mechanism has now been obtained.

The two isomers obtained from the condensation of cyanoacetamide with phenylacetone were isolated by fractional crystallization and preparative t.l.c. The physical data (Table III) are in accord with the assignment of the *cis* and *trans* structures **15a** and **b**. Isomer

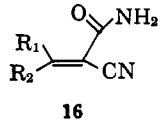


15a



15b

15a, with carboxamide *trans* to benzyl, would be the least hindered, which would account for the higher yield of **15a** from the condensation reaction and its lower solubility in ethyl acetate. The most conclusive evidence, however, is obtained from the n.m.r. data. The isomers can be assumed to be in the planar *S-cis* conformation **16** in which the carbonyl group will cause maximum deshielding of R_1.[13b] The methyl group of



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(12) (a) R. D. Campbell and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 3456 (1957); (b) N. H. Cromwell, D. B. Capps, and S. E. Palmer, *ibid.*, **73**, 1226 (1951).

(13) (a) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 139; (b) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 122–123.

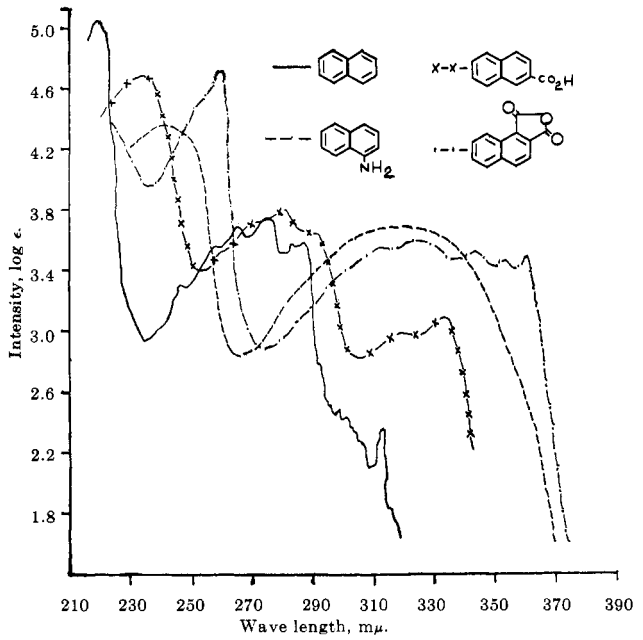


Fig. 1.—Ultraviolet spectra in ethanol.

isomer **15a** resonates 0.14 p.p.m. downfield from that of isomer **15b**, and the methylene group of isomer **15b** resonates 0.36 p.p.m. downfield from that of isomer **15a**. The magnitude of deshielding is less with the methyl group resonance because of its free rotation.[13b] The fact that the difference of chemical shifts is due to a deshielding downfield shift rather than a shielding upfield shift is supported by the corresponding δ-values of the dicyano compound **2b** (CH_3, 2.1; and $-CH_2-$, 3.8). These values agree quite well with the chemical shifts of the groups *trans* to the deshielding carbonyl group, therefore, indicating that it is the *cis* groups which are affected.

TABLE III

PROPERTIES OF ISOMERS 15a AND b

Isomer	M.p., °C.	R_f in ether	%[a] in crude product	N.m.r. peaks[b] CH_3	N.m.r. peaks[b] $-CH_2-$	N.m.r. peaks[b] Ar
15 a	140–141	0.62	56	2.29	3.85	7.2
15 b	135.5–136.0	0.75	44	2.15	4.21	7.26

[a] Calculated from the n.m.r. spectrum of crude condensation material using the ratio of peak areas. [b] Parts per million downfield from tetramethylsilane.

Isomer **15a** (cyano *cis* to aryl) was cyclized quite readily in concentrated sulfuric acid at 5° to the carboxamidoamine **3a** (Z = $CONH_2$). Isomer **15b** (carboxamido *cis* to aryl) could not be ring closed, even though it was treated at a higher temperature. These facts support the theory that the nitrile group is directly involved in the ring closure and not hydrated first to an amide.

The Ultraviolet Spectra of Substituted 1-Naphthylamines.—The cyclization of ylidenemalononitriles has made available a series of 1-naphthylamines (**3**) containing conjugatable substituents on the 2-position. A carboxamido group on the 2-position would be subject to steric hindrance by alkyl groups on the 3-position and cause inhibition of its resonance interaction with the aromatic nucleus. Such inhibition of resonance would modify the effects of extending conjugation on the various bands in the ultraviolet absorption spectra.

It has been shown that extension of conjugation in a given direction will primarily affect a band polarized in that direction. The polarization of the three bands of naphthalene (Fig. 1) are summarized in Table IV.[14]

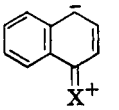
TABLE IV

POLARIZATION OF NAPHTHALENE BANDS

Band	Polarization	Wave length, mμ	Log ε
^1B_b (A)	Longitudinal[a]	221	4.98
^1L_a (B)	Transverse[b]	286	3.62
^1L_b (C)	Longitudinal	312	2.40

[a] Parallel to the long axis of the molecule. [b] Perpendicular to the long axis of the molecule.

It was further shown that a conjugatable substituent at position 1 extends conjugation in a transverse direction (species **17**) and causes bathochromic and hyperchromic effects, especially in the 285-mμ band (see 1-naphthylamine, Fig. 1). A conjugated substituent at



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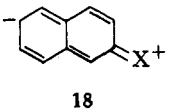

18

position 2 (species **18**) will extend conjugation in a longitudinal direction, producing bathochromic and hyperchromic effects in the two longitudinal-polarized bands, especially the C band (see 2-naphthoic acid,[15] Fig. 1).

The spectra obtained from naphthalene derivatives with conjugatable substituents in the 1- and 2-positions have been discussed by Hirschberg and Jones[15] using naphthalene-1,2-dicarboxylic acid anhydride (in *n*-heptane, Fig. 1), and various derivatives. It is evident from Fig. 1 that the spectrum of the anhydride must result from a mixture of species **17** and **18** giving the resulting red shift and intensification to all three bands of naphthalene. Bands A and C then should decrease in intensity and be shifted to shorter wave lengths in the ultraviolet spectra of compounds containing a conjugatable substituent in the 1-position and a sterically hindered conjugatable substituent in the 2-position.

In the present study, it was found that the ultraviolet spectra of the aminonitriles (Fig. 2, I–III) were similar to that of naphthalene-1,2-dicarboxylic acid anhydride. This shows the lack of inhibition of resonance in compounds II and III owing to linearity of the cyano group. The spectrum of the unhindered aminoamide (Fig. 2, IV) was found to be quite analogous to those of the aminonitriles and the anhydride. The remaining two aminoamides (V and VI) containing an alkyl group on the 3-position gave different absorption spectra. The C band found at 355–365 mμ in the spectra of the unhindered amide and nitriles was missing in the spectra of the amides V and VI, probably because of fusion with band B, which had no significant shift. Band A, at 268 mμ in the unhindered aminoamide IV, exhibited a hypsochromic shift of 30 mμ for

(14) H. H. Jaffe and Milton Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 305–307.

(15) Y. Hirschberg and R. Norman Jones, *Can. J. Research*, **27B**, 437 (1949).

the most hindered aminoamide V, and 19 mμ for VI. These data are in accord with the fact that a loss of conjugation at the 2-position will alter the longitudinal-polarized bands A and C.

Further evidence for the steric hindrance of the 2-carboxamide group was obtained from the ultraviolet spectra of the amine salts (Fig. 3, Ia–VIa). In the salt form, the unshared pair of electrons of the amine are protonated and, therefore, cannot interact with those of the nucleus. The quaternary amine then produces inductive effects analogous to those of a methyl group.[16] In the present study, the production of an amine salt would eliminate the resonance interaction of species **17** and leave only the resonance interaction of the 2-substituent. Steric hindrance of the 2-substituent would cause the absorption spectrum to approach that of an alkyl-substituted naphthalene, with a low intensity C band.

In accord with these facts, the aminonitrile salts Ia–IIIa gave absorption spectra quite analogous to that of 2-naphthoic acid (Fig. 1). Similar to the results from the free bases, the spectrum of the unhindered aminoamide salt IVa was almost identical with that of the corresponding aminonitrile salt Ia. The spectra of the hindered aminoamide salts Va and VIa, however, exhibit hypochromic and hypsochromic effects in the C band along with a large shift to shorter wave lengths in the A band.

Although the most hindered carboxamido-containing compounds V and Va absorb at shorter wave lengths for most of the peaks than the corresponding less hindered compounds VI and VIa, this would not necessarily constitute evidence for greater steric hindrance, since the difference in absorption may be due to the increased alkyl substitution of compounds VI and VIa.

Experimental[17]

Preparation of the Ylidenemalononitriles.—The method used was the same as that described in previous papers[4] following the procedure of Mowry.[1 8] The reaction conditions and physical properties of the dinitriles are listed in Table I.

Ring Closure of Phenylisopropylidenemalononitrile (2b). A.—Two grams of **2b** was dissolved in 20 ml. of concentrated sulfuric acid and allowed to stand at room temperature for 1 hr. The dark green solution was poured over 200 g. of ice and the solid was collected by filtration. Recrystallization from methanol gave 1.45 g. (73%) of **3a** (Z = CN), m.p. 146–147°; ν_{max}^{KBr} 3525, 3410, and 3250 (NH), and 2203 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38. Found: C, 78.87; H, 5.68; N, 15.47.

B.—Two grams of **2b** was dissolved in 20 ml. of concentrated sulfuric acid and heated at 90° for 1 hr., then poured over ice. No precipitate was obtained until the solution was made basic with 15% sodium hydroxide. The white solid was collected by filtration to yield 1.6 g. (73%) of **3a** (Z = $CONH_2$), m.p. 210–213°. Recrystallization from methanol gave an analytical sample, m.p. 214–215°; ν_{max}^{KBr} 3350 and 3140 (NH), and 1640 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.05; N, 4.00. Found: C, 71.91; H, 5.94; N, 14.19.

(16) R. Norman Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

(17) Melting points were taken on a Mel-Temp capillary melting point apparatus and are corrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord and n.m.r. spectra were determined in deuteriochloroform at 60 Mc. with a Varian A-60 spectrometer, employing tetramethylsilane as an internal reference. Chemical shifts are given in parts per million downfield from tetramethylsilane. The ultraviolet absorption spectra were determined with a Cary Model 14 recording spectrometer using 1-cm. sample cells.

(18) D. T. Mowry, *J. Am. Chem. Soc.*, **67**, 1050 (1945).

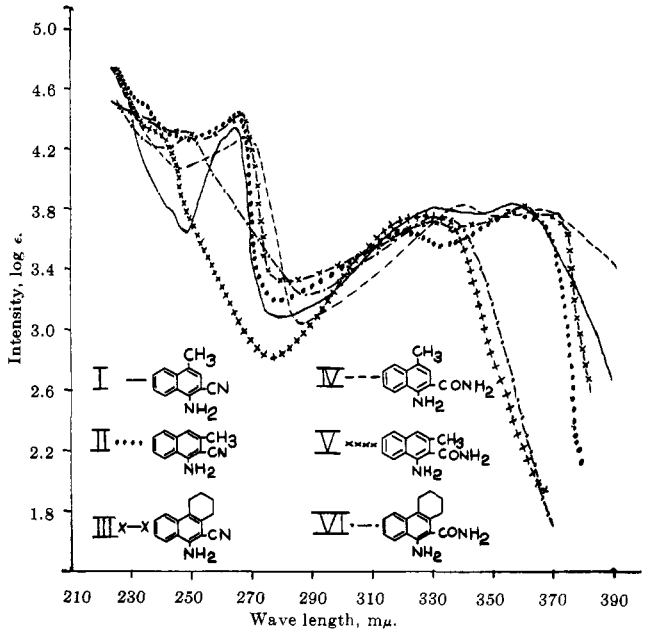

Fig. 2.—Ultraviolet spectra in 95% ethanol.

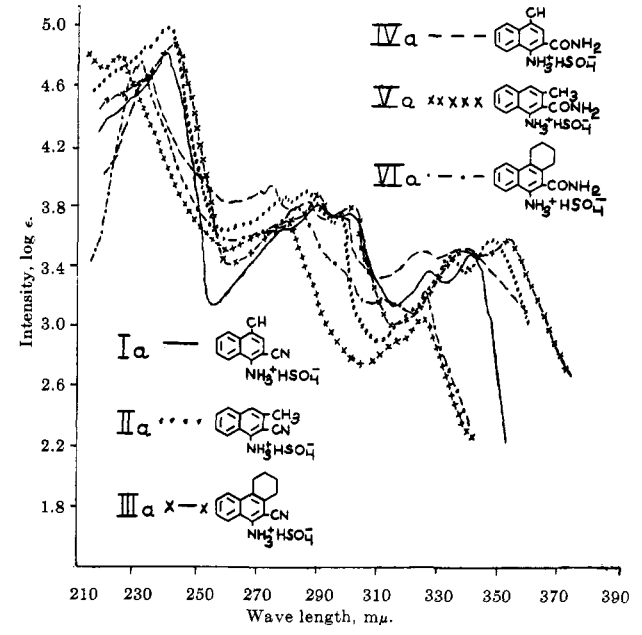

Fig. 3.—Ultraviolet spectra in 50% sulfuric acid.

Ring Closure of 2-Phenylcyclohexylidenemalononitrile (2c). A.—Two grams of **2c** was dissolved in 20 ml. of concentrated sulfuric acid and allowed to stand at room temperature for 6 hr. before pouring over ice. Filtration and subsequent recrystallization from methanol yielded 1.6 g. (80%) of **3b** (Z = CN) as colorless crystals, m.p. 165–166°; ν_{max}^{KBr} 3510, 3410, and 3290 (NH), and 2200 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.10; H, 6.41. Found: C, 80.92; H, 6.55.

B.—Two grams of **2c** treated with 20 ml. of concentrated sulfuric acid at 90° for 20 min., then poured over ice, gave 0.44 g. (22%) of **3b** (Z = CN). Basification of the acidic solution precipitated 0.02 g. (1%) of the hydrated product **3b** (Z = $CONH_2$). Recrystallization from methanol gave colorless crystals, m.p. 265–268°; ν_{max}^{KBr} 3415 and 3225 (NH), and 1630 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.98; H, 6.89; N, 11.50.

Two grams of **2c** mixed with 80 g. of polyphosphoric acid and heated at 90° for 4 hr. gave 1.3 g. (62%) of the hydrated product **3b** (Z = $CONH_2$) when poured into 500 ml. of water.

Ring Closure of 2-Phenylpropylidenemalononitrile (2d). A.—Two grams of **2d** was dissolved in concentrated sulfuric acid at 5° and kept at 5–10° for 1 hr. before pouring over ice. The white solid was collected and recrystallized from methanol to give 1.25 g. (63%) of **3c** (Z = CN), m.p. 120–121°; ν_{max}^{KBr} 3450, 3360, and 3240 (NH), and 2200 cm.$^{-1}$ (CN).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38. Found: C, 78.99; H, 5.30; N, 15.55.

B.—Two grams of **2d** placed in 20 ml. of concentrated sulfuric acid for 1 hr. at room temperature gave 1.14 g. (57%) of **3c** (Z = CN) when poured over ice. Basification of the acidic solution with 15% sodium hydroxide gave a white precipitate, which from methanol gave 0.62 g. (28%) of the hydrated product **3c** (Z = $CONH_2$), m.p. 222–224°. An analytical sample melted at 226.5–227.5°; ν_{max}^{KBr} 3410, 3320, and 3150 (NH), and 1640 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.05; N, 14.00. Found: C, 72.18; H, 6.21; N, 14.22.

C.—Two grams of **2d** was dissolved in 20 ml. of concentrated sulfuric acid and heated for 10 min. at 90°. After pouring the reaction mixture over ice, a white solid was collected by filtration. Recrystallization from methanol gave 1.32 g. (44%) of the bisulfate salt of **3c** (Z = $CONH_2$), m.p. 222–223°.

Anal. Calcd. for $C_{12}H_{14}N_2O_5S$: C, 48.32; H, 4.73; N, 9.40. Found: C, 48.38; H, 4.63; N, 9.65.

Basification of the mother liquor gave 1 g. (45%) of **3c** (Z = $CONH_2$), m.p. 223–225°. This carboxamido amine was also obtained by stirring the bisulfate salt in a solution of potassium carbonate or sodium hydroxide.

2-Cyano-3,4-diethyl-7-methoxy-1-naphthylamine (3d).—One gram of **2e** was mixed with 20 ml. of polyphosphoric acid and heated at 120° for 20 min. After cooling to 80°, the deep red solution was poured into 50 ml. of ice–water. Filtration gave 0.4 g. of red-brown solid. Neutralization of the acidic solution gave no further product. The solid was dissolved in chloroform and placed on a column packed with activated alumina. Elution with chloroform–methanol (95:5) gave 0.1 g. (10%) of red crystals, m.p. 170–180°. Recrystallization from benzene–hexane gave an analytical sample, m.p. 189–191°; ν_{max}^{KBr} 3350 and 3370 (NH), and 2200 cm.$^{-1}$ (CN); $\lambda_{max}^{95\% \text{ ethanol}}$ mμ (log ε): 220–230 sh (4.09), 246 (4.14), 260 sh (4.07), and 345–350 (3.99).

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.13; N, 11.02. Found: C, 75.46; H, 7.31; N, 11.12.

Attempted Cyclization of α-Naphthylmethylidenemalononitrile (5a).—Three grams of **5a** was dissolved in 30 ml. of concentrated sulfuric acid, heated on a steam bath for 10–15 min., and then poured over 300 g. of crushed ice. The solid that formed was collected by filtration. Ether extraction and neutralization of the acidic solution produced no other material. Recrystallization of the solid from benzene gave white plates, 1.5 g. (45%), of **6a**, m.p. 194–196°; ν_{max}^{KBr} 3535 and 3255 (NH), 2240 (CN), and 1670 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.67; H, 4.51; N, 12.61. Found: C, 75.37; H, 4.59; N, 12.66.

The mixture melting point of **6a** and the condensation product from α-naphthaldehyde and cyanoacetamide was not depressed.

Attempted Cyclization of 1-(α-Naphthyl)ethylidenemalononitrile (5b). A.—Two grams of **5b** was added to 20 ml. of concentrated sulfuric acid and allowed to stand at room temperature for 1 hr. before pouring over ice. The orange solid (2 g.) was collected by filtration and placed on a column packed with silica gel. Elution with chloroform gave 160 mg. of a dark red-brown solid, m.p. 110–115°. Further elution with chloroform–methanol solutions produced 1.12 g. of uncharacterized tars. The dark red-brown solid was purified on preparative t.l.c. plates using Silica Gel H developed with chloroform to give 90 mg. (4%) of a yellow powder, m.p. 140–150°. It could not be recrystallized from various organic solvents. The infrared spectrum indicates the powder to be compound **8b**: $\nu_{max}^{CHCl_3}$ 3390 and 3310 (NH), 1695 (CO), and 1660 and 1640 cm.$^{-1}$ (amide CO).

B.—The crude product obtained from a reaction carried out under conditions similar to part A was sublimed at 100° (1 mm.). A red solid was obtained and recrystallized from acetic acid to give 40 mg. (2%) of red crystals, m.p. 67–69°. The infrared spectrum supports the assignment of structure **8a**: ν_{max}^{KBr} 2210 (CN) and 1710 cm.$^{-1}$ (CO). The n.m.r. spectrum showed a peak at δ 2.74 (CH_3) along with a complex multiplet for the aromatic hydrogens at δ 7.5–8.2.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 82.21; H, 4.14. Found: C, 82.40; H, 4.49.

C.—One gram of **5b** was heated in 20 g. of polyphosphoric acid on a steam bath for 3 hr. and poured over ice. Polymeric material melting above 300° was obtained by filtration. Extraction of the diluted acidic solution with chloroform yielded 140 mg. of white **6c**, m.p. 229–231° (from ethanol); ν_{max}^{KBr} 3401 and 3160 (NH), and 1665 and 1645 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.98.

D.—One gram of **5b** was heated in 20 g. of polyphosphoric acid on a steam bath for 1 hr. and poured over ice. Chloroform extraction of the acidic solution gave 50 mg. of **6b**, m.p. 208–210° (from ethanol); ν_{max}^{KBr} 3410 and 3200 (NH), 2217 (CN), and 1665 cm.$^{-1}$ (amide CO). The n.m.r. spectrum showed a peak at δ 2.81 for 3 protons.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.08. Found: C, 75.92; H, 5.24.

E.—A solution of 2 g. of **5b**, 10 ml. of dimethylformamide, and 10 ml. of concentrated sulfuric acid was stirred for 1 hr. at room temperature. The dark solution was poured over ice, and the resulting precipitate was collected by filtration. Unchanged starting material (1.5 g.) was obtained by washing the precipitate with ether and evaporating the ether extract. The residue not soluble in ether was recrystallized from ethanol to give 0.24 g. of colorless crystals of **6b**, m.p. 209–210°. The mixture melting point with the sample obtained in part D was undepressed.

α-Naphthylmethylmalononitrile (9).—A mixture of 10 g. of α-naphthylmethylidenemalononitrile (**5a**), 0.4 g. of platinum oxide, and 250 ml. of absolute ethanol was subjected to 45 p.s.i. of hydrogen for 3 hr. The catalyst was filtered, and the solvent was evaporated *in vacuo* to leave 9.5 g. of a dark oil. The oil crystallized on cooling and was recrystallized from 95% ethanol to give 7.23 g. (72%) of **9**, m.p. 63–64°. An analytical sample had m.p. 67–68°; ν_{max}^{KBr} 2210 and 2290 cm.$^{-1}$ (CN); the n.m.r. spectrum showed AB_2 pattern[19] centered at δ 3.82 and 3.69.

Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.52; H, 4.89; N, 13.59. Found: C, 81.57; H, 5.10; N, 13.21.

Attempted Ring Closure of 9. A.—One gram of **9** was dissolved in concentrated sulfuric acid and allowed to stand at room temperature for 2 hr. before it was poured over ice. No product could be obtained by extraction of the acidic solution with chloroform or by adding base and extracting the basic solution.

B.—Two grams of **9** was placed in 40 g. of polyphosphoric acid and heated at 120° for 0.5 hr. It was cooled to 80° and poured over ice. The precipitate was collected by filtration and recrystallized from methanol to give 1.4 g. (60%) of **10**, m.p. 255–260°. Further recrystallizations from acetic acid–water gave colorless crystals, m.p. 267–269°; ν_{max}^{KBr} 3400 and 3210 (NH), and 1670 and 1650 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 68.84; H, 5.89; N, 10.93. Found: C, 69.16; H, 5.96; N, 11.57.

2-Cyano-3-methyl-4-phenylbutyronitrile (11).—A solution of 10 g. of phenylisopropylidenemalononitrile (**2b**) in 200 ml. of absolute ethanol was shaken under hydrogen at 3 atm. with 0.4 g. of platinum oxide in a Parr low-pressure hydrogenation apparatus. The catalyst was filtered and the solvent was evaporated *in vacuo* to yield an oil residue. Distillation under reduced pressure gave 8.1 g. (80%) of a colorless liquid, b.p. 103–105° (0.01 mm.); ν_{max}^{film} 2280 and 2270 cm.$^{-1}$ (CN); n.m.r. spectrum showed a doublet at δ 1.3 (J = 6 c.p.s., 3 protons), complex multiplet from 2.16–2.58 (1 proton), doublet at 2.8 (J = 6 c.p.s., 2 protons), doublet at 3.54 (J = 5 c.p.s., 1 proton), and complex multiplet from 7.17–7.42 (5 protons).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.21; H, 6.57; N, 15.21. Found: C, 78.27; H, 6.45; N, 15.50.

2-Carboxamido-3-methyl-1-tetralone (12).—Two grams of **9** was stirred in 15 ml. of concentrated sulfuric acid for 4 hr. and poured over ice. The orange solid was collected by filtration and recrystallized from 95% ethanol to give 1.31 g. (60%) of **12**, m.p. 182–183°. An analytical sample had m.p. 183–184°; ν_{max}^{KBr} 3400 and 3200 (NH), 1670 (CO), and 1640 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.45; N, 6.90. Found: C, 71.18; H, 6.35; N, 6.97.

The **2,4-Dinitrophenylhydrazone** of **12** melted at 225–227°.

Anal. Calcd. for $C_{18}H_{17}N_5O_5$: N, 18.27. Found: N, 18.48.

Condensation of Cyanoacetamide with Phenylacetone to Give 15a and 15b.—A mixture of 80 g. (0.6 mole) of phenylacetone, 50.4 g. (0.6 mole) of cyanoacetamide, 4.62 g. of ammonium acetate, 7.2 g. of glacial acetic acid, and 60 ml. of benzene was refluxed overnight in a system with a Dean–Stark trap. The

(19) Ref. 13, p. 93, Fig. 6.7c.

reaction mixture was cooled and filtered to yield 104 g. of crude product, m.p. 75–87°. Concentration of the mother liquor afforded another 10 g. of product. Development of the crude product on Silica Gel G plates with ether gave two spots, R_f 0.62 and 0.75. Recrystallization of the crude product from ethyl acetate–hexane five times gave only the less soluble isomer **15a**, m.p. 140–141°; R_f 0.62; ν_{max}^{KBr} 3390, 3300, and 3200 (NH), 2210 (CN), and 1680 cm.$^{-1}$ (amide CO).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.05; N, 14.00. Found: C, 71.97; H, 6.04; N, 14.30.

The soluble isomer **15b** was obtained by evaporating the mother liquor from the recrystallizations of isomer **15a** and placing 100 mg. of the residue on preparative Silica Gel G plates (1.5 mm. thick). Development with ether and extraction of the top band with acetone gave 50 mg. of isomer **15b**, m.p. 135.5–136°, R_f 0.75. The mixture melting point with isomer **15a** was 105–109°. The infrared spectrum in chloroform was identical with that of isomer **15a** in chloroform, but the spectrum of the KBr mull differed: ν_{max}^{KBr} 3410, 3350, 3300, and 3160 (NH), 2210 (CN), and 1680 cm.$^{-1}$ (amide CO).

Ring Closure of Isomer 15a.—One gram of isomer **15a** was dissolved in 5 ml. of concentrated sulfuric acid at 5° and maintained between 5–10° for 15 min. The green solution was poured over ice. No precipitation occurred until the solution was neutralized with 15% sodium hydroxide. The white solid (0.98 g., m.p. 175–190°) was collected by filtration and recrystallized from methanol to give 0.48 g. (48%) of **3a** (Z = $CONH_2$). A mixture melting point with a sample obtained by ring closure of **2b** was undepressed and their infrared spectra were identical.

Attempted Ring Closure of Isomer 15b.—A solution of 0.47 g. of isomer **15b** and 4 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 2.5 hr. before pouring over ice. The precipitate was collected to give 0.27 g. of starting material, m.p. 115–120°. This was confirmed by identical infrared spectra and R_f values on t.l.c. Neutralization of the acidic mother liquor did not yield any precipitate.

A New Sesquiterpene Lactone with Analgesic Activity from *Helenium amarum* (Raf.) H. Rock

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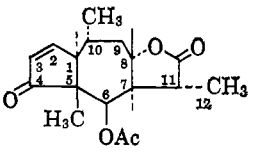
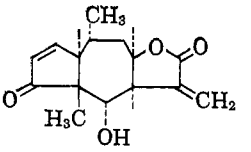
A new sesquiterpene lactone with potent analgesic activity has been isolated from *Helenium amarum* (Raf.) H. Rock. The structure of this substance has been shown to be Ia by correlation with another accompanying lactone (III), which in turn was related to desacetyldihydroisotenulin (XII). The activity of a number of related substances was investigated.

In connection with our general medicinal plant screening program, we had occasion to submit a crude extract of *Helenium amarum* (Raf.) H. Rock[1] to broad pharmacological investigation.[2] On subcutaneous administration, this material was found to have an analgesic activity in mouse tail flick test[3] which was not antagonized by nalorphine. It was also shown to inhibit the writhing syndrome in mice induced by the intraperitoneal injection of acetic acid. Further, the extract demonstrated no anticonvulsant properties nor did it cause any alteration in spinal reflexology in cats.

The above combination of biological properties seemed to warrant an attempt to identify the chemical individual responsible for this activity. The use of solvent distribution and of chromatographic techniques led to the isolation of two new substances. One, which we have called amaralin, $C_{15}H_{20}O_4$, m.p. 195–198°, $[\alpha]^{25}D$ +5°, was responsible for the major part of the analgesic action. The other, later shown to be identical with aromaticin,[4] $C_{15}H_{18}O_3$, m.p. 234–236°, $[\alpha]^{26}D$ +14°, was inactive. There also was a relatively large quantity of tenulin known to be the main sesquiterpene lactone of *Helenium amarum* (Raf.) H. Rock.[5] The empirical formulas of the two new substances indicated that they, too, were probably sesquiterpenes and, therefore, possibly related structurally to isotenulin or to helenalin.[6]



Isotenulin



Helenalin

That amaralin had one hydroxyl group could be inferred from its infrared absorption at 3430 cm.$^{-1}$ and by the formation of a monoacetate (Ib), which no longer had an infrared absorption in the hydroxyl region. This was further supported by the observed downfield shift of the n.m.r. signal at 3.81 p.p.m. in amaralin to 4.71 p.p.m. in the acetate (Table I). Such a shift would be expected for a proton attached to a carbon bearing a secondary alcohol.

Another band in the amaralin infrared spectrum at 1736 cm.$^{-1}$ could be attributed to a cyclic ketone or to a γ-lactone containing a conjugated exocyclic methylene, a grouping which is characteristic of many of these sesquiterpene lactones.[5] That this system was actually present in amaralin was further indicated by infrared bands at 1660 and 940 cm.$^{-1}$ (exocyclic double bond α

(1) The plant material was collected and identified by Harry E. Ahles, Botany Department, University of North Carolina, Chapel Hill, N. C., to whom our sincere thanks are due.

(2) We wish to express our appreciation to Dr. A. Plummer and his associates of our Macrobiology Division for the biological tests and for their kind permission to include some of their results in this paper.

(3) L. Witkin, C. Huebner, F. Galdi, E. O'Keefe, P. Spitaletta, and A. Plummer, *J. Pharmacol. Exptl. Therap.*, **133**, 400 (1961).

(4) During the preparation of the manuscript of this paper, an article by J. Romo, P. Joseph-Nathan, and F. Diaz A. [*Chem. Ind.* (London), 1839 (1963)] appeared in which the isolation and structure of a new sesquiterpene lactone, aromaticin, was described. The physical properties of this substance corresponded with our second lactone and the methods of structure proof were exactly the same. A comparison sample of aromaticin kindly supplied by Dr. Romo through the courtesy of Dr. W. I. Taylor was shown to be identical with our substance by the usual criteria.

(5) For a review of the excellent and comprehensive work already done on the constituents of this and related species, see (a) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *J. Am. Chem. Soc.*, **85**, 19 (1963); (b) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, **19**, 1359 (1963); and (c) W. Herz, *J. Org. Chem.*, **27**, 4043 (1962), and related papers.

(6) For simplicity in the development of our structural arguments we will assume this relationship, later to be demonstrated, and use the numbering system shown when referring to particular carbon and hydrogen atoms.