ether was added dropwise at room temperature to an equimolar mixture of an alkyl isocyanide and a Schiff base of benzaldehyde in 10 ml of ethyl ether. A white precipitate appeared immediately. The reaction system was kept at room temperature for 1 day. Then a water–methanol mixture was added to terminate the reaction. The precipitate was washed with petroleum ether, extracted with chloroform and finally recrystallized from acetone.

**N,N′-Diphenyl-1-phenyl-2-cyclohexyliminoethylenediamine (II).**—A solution of 20 mmol of $BF_3 \cdot OEt_2$ in 5 ml of ethyl ether was added dropwise at 0° to a solution of 30 mmol of cyclohexyl isocyanide and benzylidene aniline in 30 ml of ethyl ether. After standing 1 day at the same temperature, the reaction was stopped by the addition of a water–methanol mixture. From the ether-soluble part, 1.5 g of II was obtained by recrystallization: yield 13% (based on isocyanide); mp 136–137°; nmr (in $CCl_4$) $\tau$ 2.5–3.8 (phenyl, multiplet, 15 H), 4.30 (NH, multiplet, 1 H), 5.08 (CH, singlet, 1 H), 6.15 (CH of cyclohexyl ring, multiplet, 1 H), 6.30 (NH, multiplet 1 H), 7.8–9.0 ($CH_2$ of cyclohexyl ring, multiplet, 10 H). *Anal.* Calcd for $C_{26}H_{29}N_3$: C, 81.42; H, 7.62; N, 10.96. Found: C, 81.07; H, 7.81; N, 10.79.

**N-Cyclohexyl-2-(methylamino)-2-phenylacetamide (III).**—At 0°, 2.73 g of cyclohexyl isocyanide (25 mmol) was added dropwise to a mixture of 3.18 g of benzaldehyde (30 mmol), 3 ml of methylamine (30% in water, 30 mmol), 3 ml of 10 *N* HCl and 5 ml of methanol. After standing for 1 hr, the reaction system was acidified with 20 ml of 2 *N* HCl, and extracted with benzene. The water layer was neutralized with 10 ml of 40% aqueous NaOH and extracted with methylene chloride. From the methylene chloride soluble part, 1.91 g of III was obtained by recrystallization from 1:5 benzene–petroleum ether (bp 30–60°): yield 31%; mp 82–83°; nmr (in $CDCl_3$) $\tau$ 2.68 (phenyl, singlet, 5 H), 5.97 (CH, singlet, 1 H), 7.55 ($CH_3$, singlet, 3 H), 8.0–9.0 ($CH_2$ of cyclohexyl ring, multiplet, 10 H). *Anal.* Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.18; H, 9.09; N, 11.15.

**Registry No.**—Ia, 18742-13-7; Ib, 18742-14-8; Ic, 18742-15-9; II, 18742-16-0; III, 18742-17-1.

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# Synthesis of the N-Isobutylamide of All-*trans*-2,6,8,10-Dodecatetraenoic Acid

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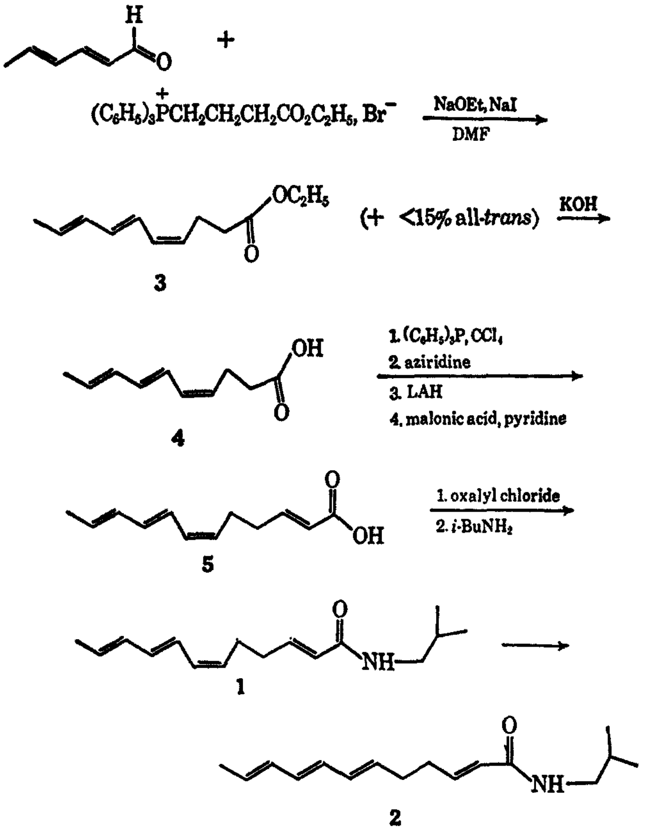
An insecticidal component of American coneflower roots, *Echinacea angustifolia* D.C. and *E. pallida* (Nutt.) Britton (Compositae), has been assigned structure 1.[1] This same material occurs also in the barks of southern prickly ash, *Zanthoxylum clava-herculis* L.,[2] and the Japanese tree, *Zanthoxylum piperitum* D.C. (Rutaceae).[3] These isolates have been named echinacein, neoherculin, and α-sanshool, respectively. The instability of the material makes purification a formidable problem. The only criterion of purity has been ultraviolet absorption, and there is contamination with the all-*trans* isomer, 2, which merely changes the extinction coefficients and not the position of the maxima. Treatment of the purified natural insecticide with iodine and uv light produces a crystalline substance of higher melting point, slightly greater maximum uv extinctions, and slightly lower insecticidal activity. This material, β-sanshool, has been assigned the all-*trans* configuration.[3]

We have synthesized 1, containing an estimated 30% of the 6-*trans* isomer (Chart I). Studies by Bergelson and coworkers have revealed that Wittig condensations conducted in DMF using alkoxides to generate the ylides produced olefins which were 91–93% *cis*.[4] In addition, they synthesized ethyl α-eleostearate, a conjugated *cis,trans,trans*-triene in this same manner by using the required *trans,trans*-dienal as the starting aldehyde.[5] We employed commercial sorbic aldehyde (>97% *trans* by glpc) and the triphenylphosphonium salt derived from ethyl-4-bromobutyrate. Triene ester 3 was uniform by glpc and was estimated to contain no more than 15% of the all-*trans* isomer using the uv data available for α- and β-eleostearic acids (see Table I). Saponification to the free acid 4 was followed by conversion into the aziridide *via* the acid halide. The usual methods for preparing acid halides were unsuccessful, and the method described by Lee[6] using triphenylphosphine and carbon tetrachloride was used instead. The aziridide was reduced with $LiAlH_4$ to the aldehyde which was then transformed into the required acid, 5,



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(1) M. Jacobson, *J. Org. Chem.*, **32**, 1646 (1967).

(2) L. Crombie, *J. Chem. Soc.*, 995 (1955).

(3) L. Crombie and J. D. Shah, *ibid.*, 4244 (1955); L. Crombie and J. L. Tayler, *ibid.*, 2760 (1957).

(4) L. D. Bergelson, V. A. Vaver, V. Yu Kovtun, L. B. Senyavina, and M. M. Shemyakin, *Zh. Obshch. Khim.*, **32**, 1802 (1962).

(5) L. D. Bergelson, V. D. Solodovnik, and M. M. Shemyakin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1315 (1962); *Chem. Abstr.*, **58**, 7824 (1963).

(6) J. B. Lee, *J. Amer. Chem. Soc.*, **88**, 3440 (1966).

TABLE I

UV SPECTRAL DATA[a]

| Compd | Maxima, λ (ε) | | |
|---|---|---|---|
| 3 | 258.5 (37,800) | 267 (48,900) | 277 (39,500) |
| 4 | 258 (38,600) | 267 (52,200) | 277.5 (41,100) |
| 5 | 260 (36,500) | 268 (48,000) | 278.5 (37,900) |
| 1 | 260 (37,900) | 268.5 (49,400) | 278.5 (39,900) |
| α-Sanshool[b] | 260 (36,000) | 269 (47,000) | 278.5 (37,500) |
| 2 | 257.5 (41,800) | 266 (55,900) | 276.5 (44,000) |
| β-Sanshool[b] | 259 (38,500) | 267.5 (48,500) | 278 (39,000) |
| α-Eleostearic acid[b] | 261 (36,000) | 271 (47,000) | 281 (38,000) |
| β-Eleostearic acid[b] | 259 (49,000) | 268 (61,000) | 279 (49,000) |
| Isobutylamide of β-eleostearic acid[b] | 258 (42,000) | 268 (58,500) | 278 (43,500) |

[a] Spectra were determined in absolute EtOH with a Beckman DK-2 spectrophotometer. [b] Reference 3.

by means of the Doebner–Miller condensation in pyridine solution. Conversion of **5** into its acid halide was accomplished quite cleanly with oxalyl chloride, and this compound upon treatment with isobutylamine produced **1**. If the uv data for α-sanshool represents that of geometrically pure **1**, and the data for the N-isobutylamide of β-eleostearic acid represents the spectrum of **2**, the synthetic **1** contains ~30% of the all-*trans* compound. A maleic anhydride adduct of synthetic **1** had virtually the same melting point as those of echinacein and α-sanshool. No direct comparison could be made although the infrared spectral properties of the tetraene and its maleic anhydride adduct were quite similar to those reported. The synthetic material was a mild sialagog and very toxic to adult house flies, *Musca domestica* L., exhibiting a rapid high knockdown and considerable mortality.

Treatment of **1** with a trace of iodine in hexane and uv light as described[1] first produced a crystalline deposit and then a yellow gum. However, exposure for 10 min to ordinary laboratory light did provide the all-*trans* compound. Although its melting point was lower and broader than that described,[1,3] the uv spectrum is much more consistent with that of the N-isobutylamide of β-eleostearic acid than is the spectrum reported for β-sanshool.

It was noted that the triene ester **3** could be obtained with the same purity (uv of the ester, melting point of the acid) by carrying out the condensation in THF or DME with NaH.

## Experimental Section

Infrared spectra were determined with a Perkin-Elmer Model 521 infrared spectrophotometer. Gas chromatograms were obtained with an Aerograph Model A-700 instrument. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Company and trade names are given for identification purposes only and do not constitute endoresement by the U.S. Department of Agriculture.

**Ethyl 4,6,8-Decatrienoate (3).**—Dry DMF (50 ml) was added to NaOEt obtained from 0.92 g of Na and placed under $N_2$. The triphenylphosphonium salt of ethyl 4-bromobutyrate (18.24 g), and NaI (6.00 g) were added, and the resulting solution was stirred for 1 hr. When sorbaldehyde (2.40 g) was added, the temperature rose to ~45°. The mixture was then allowed to stand overnight at ambient temperature after which it was diluted with water and extracted with ether. The ether solution was washed and dried ($MgSO_4$), the ether was removed under reduced pressure, and the product was triturated several times with hexane. The hexane was removed under reduced pressure, and the product was distilled to give 2.32 g (29.9%) of **3**, bp 82–86° (00.7 mm). Glpc showed one peak (5% silicone gum rubber SE-30 on base-washed Chromosorb P, 6 ft × 0.25 in., and 20% Carbowax 20M on Chromosorb W, 5 ft × 0.25 in.); ir ($CCl_4$) 1737 (ester C=O), 994 s and 966 $cm^{-1}$ w (conjugated triene).

*Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.12; H, 9.35.

This compound, as well as others prepared, was unstable and was best stored under $N_2$ at 0° with a trace of hydroquinone added to all materials that were to be distilled. Preparation of **3** could be accomplished in yields of 26–44% by using anhydrous THF or DME with 1 equiv of NaH. These reactions were allowed to proceed overnight at room temperature under $N_2$.

**4,6,8-Decatrienoic Acid (4).**—Ester **3** (14.0 g) was added to a solution of 15.7 g of KOH in 240 ml of 3:1 EtOH–$H_2O$ under $N_2$ and stirred at room temperature for 1 hr. The mixture was diluted with $H_2O$ and extracted with ether, and the aqueous phase was acidified with cold 3 *N* HCl and extracted with ether. The extract was dried ($MgSO_4$–$NaHCO_3$), concentrated, and distilled to give 10.2 g (85.4%) of liquid: bp 115–130° (0.15 mm); ir (film) 1710 (acid C=O), 992 and 965 $cm^{-1}$ (conjugated triene); mp 46–50° (petroleum ether, bp 30–60°).

*Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.09; H, 8.60.

**2,6,8,10-Dodecatetraenoic Acid (5).**—Acid **4** (9.0 g) and 14.4 g of triphenylphosphine were dissolved in 150 ml of $CCl_4$, placed under $N_2$, and heated under reflux overnight. The solvent was removed under reduced pressure, and the product was taken up in hexane and filtered. The precipitate was washed with hexane, and the combined filtrate was concentrated and employed directly for the next step: ir (film) 1795 (acyl C=O), 1734 $cm^{-1}$ (contaminant).

The acid halide was added to an ice-cold solution of 2.36 g of ethylenimine and 5.56 g of triethylamine in 200 ml of anhydrous ether. The mixture was allowed to come to room temperature. Then after 1 hr, it was washed with water, dilute HCl, and water. The organic phase was dried ($MgSO_4$–$NaHCO_3$) and concentrated: ir (film) 1690 (aziridide C=O), 992 and 963 $cm^{-1}$ (conjugated triene).

The crude aziridinde was added to a slurry of 1.05 g of $LiAlH_4$ in 125 ml of anhydrous ether at <10°, the mixture was stirred at 0–10° for 0.5 hr, and cold 5% $H_2SO_4$ was added. Then, after 20 min, the layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated: ir (film) 2690 (aldehyde C–H), 1710 (C=O), 990 and 962 $cm^{-1}$ (conjugated triene).

The crude aldehyde was dissolved in 14 ml of anhydrous pyridine containing 5.72 g of malonic acid and 10 drops of piperidine. The mixture was allowed to stand overnight under $N_2$ at room temperature and then heated under reflux for 2 hr. The mixture was cooled, poured into cold 2.5 *N* HCl, and extracted with ether. The extract was washed with dilute base, and the aqueous phase was acidified and extracted with ether. The extract was dried ($MgSO_4$) and concentrated to give 4.5 g (43%) of acid **5** as a tan solid. Recrystallization from hexane produced colorless needles: mp 93.5–95°; ir ($CCl_4$) 1698 (α,β-unsaturated acid C=O), 1650 (conjugated C=C), 992 and 963 (conjugated triene), and 974 $cm^{-1}$ (*trans* C=C conjugated with C=O).

**Isobutylamide of *trans,cis(trans),trans,trans*-2,6,8,10-Dodecatetraenoic Acid (1).**—Acid **5** (300 mg) freshly recrystallized from hexane was dissolved in 15 ml of anhydrous ether containing 0.38 ml of oxalyl chloride. The solution was allowed to stand overnight under $N_2$ and then concentrated with hexane to remove excess oxalyl chloride to give crude acid halide: ir (film) 1750 (acyl C=O), 1625 (C=C), 992 and 965 (conjugated triene, *trans* C=C conjugated to C=O, *i.e.*, 965 is a composite).

The acid halide was added to an ice-cold solution of 117 mg of isobutylamine and 161 mg of triethylamine in anhydrous ether. The product was obtained as described for the aziridide to give, upon crystallization from petroleum ether (bp 30–60°), 299 mg (77.6%) of nearly white powder: mp 61–63° (lit.[1] mp 69° for echinacein); ir ($CCl_4$) 3450, 3290, 3070 (N–H) 1670 (amide I) 1630 (C=C), 1542 (amide II), 990 and 965 $cm^{-1}$ (conjugated triene and *trans* C=C conjugated to C=O). The adduct with maleic anhydride was prepared by heating in $N_2$ atmosphere in toluene under reflux overnight: mp 100–102°, after recrystallization from ether–petroleum ether (lit.[1] mp 99–100°); ir (Nujol mull) 3340, 3125, 3030, 1846, 1766, 1666, 1542, 976, sh 966 $cm^{-1}$ w. This last named band represents unconjugated *trans* olefin, which confirms the contamination in this adduct by the adduct of the all-*trans* isomer.

*Anal.* Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.30; H, 7.96; N, 4.04.

**Isobutylamide of *trans,trans,trans,trans*-2,6,8,10-Dodecatetraenoic Acid (2).**—Amide 1 (108 mg) was dissolved in 25 ml of hexane (containing a few milliliters of ether to aid solution), a trace of $I_2$ was added, and the solution was kept under $N_2$ for 10 min. The mixture was chilled and filtered to give, after recrystallization from hexane, 74 mg (72%) of white needles: mp 100–111°; ir ($CCl_4$) 3450, 3300, 3115 (NH), 1680 (amide I), 1638 (C=C), 992 and sh 970 (conjugated triene and C=C conjugated to C=O; the latter band is again composite). The maleic anhydride adduct was prepared as before: mp 160.5–163°, after recrystallization from THF–hexane (lit.[1] mp 149–150°); ir (Nujol mull) 3335, 3030, 1845, 1766, 1666, 1544, 976 and 963. The last two bands named represent the expected conjugated and unconjugated *trans* C=C absorptions.

*Anal.* Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.36; H, 7.84; N, 3.99.

**Registry No.**—1, 504-97-2; 1 (maleic anhydride adduct) 18744-22-4; 2, 10076-00-3; 2 (maleic anhydride adduct), 18744-23-5; 3, 18744-19-9; 4, 18744-20-2; 5, 18744-21-3.

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# Bicyclic Ketones. II. Abnormal Reduction of Umbellulone[1]

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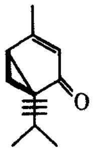
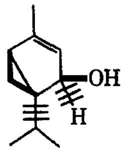
Stereoselective metal hydride reducing agents have become an important asset to the synthetic organic chemist.[2] Although abnormal reduction with these reagents is well established,[3] the metal hydride reduction of umbellulone[4] (1) affords a spectrum of abnormal reductions with reagents that are otherwise either stereoselective or often stereospecific.

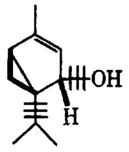
As a synthetic entrance into certain tricyclic ketones, we wished to prepare umbellulols 2 and 3. It was anticipated that the least selective reducing agent for this purpose would be lithium aluminum hydride. That expectation was fulfilled, the products of the reaction being a 7:3 mixture of unsaturated alcohols 2 and 3. The assignment of configuration of these alcohols will be deferred until later.



1



2



3

Attempted reduction of umbellulone to 2 and 3 with more stereoselective reducing agents led to the results in Table I.

That these anomalous results are due, in large degree, to the presence of the bicyclic system can be seen by a comparison with the results in Table II. These results are analogous reductions of the α,β-unsaturated ketones, piperitone (6) and pulegone (7).

An inspection of a Drieding model of umbellulone leads to the conclusion that the α side of the molecule (steroid nomenclature) produces considerably less steric interaction to an incoming nucleophile than the β side (isopropyl group *vs.* cyclopropyl). If the incoming nucleophile is large, however, both sides are sterically hindered. The smaller lithium aluminum hydride has little trouble effecting a normal reduction of the carbonyl group without affecting the double bond that is conjugated to it. No 1,4 reduction is observed with this reagent unless a large excess of reducing agent is used. The much bulkier lithium aluminum tri-*t*-butoxyhydride is not able to approach the carbonyl group and is restricted to a 1,4 addition to the conjugated system leading to dihydroumbellulone (5) as the major product. In view of the unanticipated reduction of umbellulone to dihydroumbellulols 4 by sodium borohydride in methanol, one must conclude that this reducing agent is highly solvated preventing normal addition to the carbonyl group. That this reduction is indeed a 1,4 addition followed by further reduction to 4 is confirmed by the nonreducibility of umbellulols 2 and 3 under the same reaction conditions. Lithium borohydride, while not so useful as lithium aluminum hydride, leads predominantly to umbellulols 2 and 3.

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(1) (a) Abstracted from the M.S. Thesis of R. H. Chung, Howard University, 1968. (b) Bicyclic Ketones. I: J. W. Wheeler, R. H. Chung, Y. N. Vaishnav, and C. C. Shroff, *J. Org. Chem.*, **34**, 545 (1969).

(2) H. O. House, "Modern Synthetic Reactions," Benjamin Publishing Co., New York, N. Y., 1965, Chapter 2; "Steroid Reactions, An Outline for Organic Chemists," C. Djerassi, Ed., Holden-Day Inc., San Francisco, Calif., 1963, Chapter 2.

(3) The most frequent exception to the rule that carbon–carbon double bonds are inert to reduction are β-aryl-α,β-unsaturated carbonyl compounds. See, for example, R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948); F. A. Hochstein and W. G. Brown, *ibid.*, **70**, 3483 (1948); M. J. Jorgenson, *Tetrahedron Lett.*, No. 13, 559 (1962). For other examples, see H. Shechter, D. E. Ley, and E. B. Roberson, Jr., *J. Amer. Chem. Soc.*, **78**, 4984 (1956); C. Djerassi and W. Rittel, *ibid.*, **79**, 3528 (1957); E. Schenker, *Angew. Chem.*, **73**, 81 (1961); W. J. Bailey and M. E. Hermes, *J. Org. Chem.*, **29**, 1254 (1964); J. A. Marshall and R. D. Carroll, *ibid.*, **30**, 2748 (1965).

(4) The absolute configuration of umbellulone has been established by T. Norin [*Acta Chem. Scand.*, **16**, 640 (1962)], and by H. Smith and A. Gordon [*J. Amer. Chem. Soc.*, **84**, 2840 (1962)].