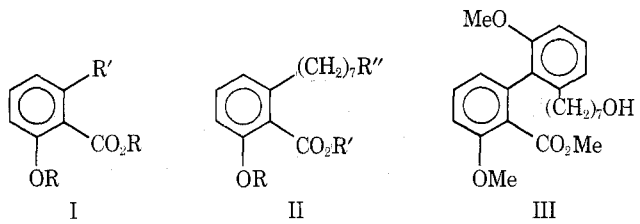
Communications

Synthesis of 6-[8′-(*Z*)-Pentadecenyl]salicylic Acid, "Anacardic Acid Monoene" (Ginkgolic Acid)

Summary: 3-Fluoroanisole has been used in a novel aryne type reaction with the lithium derivative of (OH-protected) 7-chloroheptan-1-ol and subsequent further reaction steps for the synthesis of 6-[8′-(*Z*)-pentadecenyl]salicylic acid.

Sir: By means of a novel aryne synthesis the *Z* monoene of the C-15 anacardic acid series (ginkgolic acid,[1] "anacardic acid monoene") (I, R = H; R′ = $C_{15}H_{29}$) has been synthesized. Anacardic acid[2] (I, R = H; R′ = $C_{15}H_{31-n}$, n = 0, 2, 4, 6) occurs widely as the major phenolic component in *Anacardium occidentale* and is a precursor of the industrially useful cardanol[3] formed by thermal decarboxylation. Similar substances are anagigantic acid[4] (I, R = H; R′ = $C_{11}H_{23}$), pelandjauic acid[5] (I, R = H; R′ = $C_{17}H_{35-n}$, n = 0, 2, 4, 6), hydroginkgolinic acid[6] (I, R = H; R′ = $C_{14}H_{29}$), and frutescin[7] (I, R = Me; R′ = $CH_2C{=}CC{\equiv}CCH_3$), one of five related structures. 1,7-Heptanediol was converted into 7-chloroheptan-1-ol with hot concentrated hydrochloric acid.[8] Interaction with ethyl vinyl ether in the presence of *p*-toluenesulfonic acid gave the ethyl 7-chloroheptyl acetal of acetaldehyde which reacted with lithium at 0° and subsequently with 3-fluoroanisole to yield after carbonation[9] and acid-catalyzed methanolysis, followed by selective methylation (ethereal diazomethane at 0°), methyl 6(7′-hydroxyheptyl)salicylate *O*-methyl ether (II, R = R′ = Me; R′ = OH), accompanied by the diphenyl compound III,[10]



I II III

and a negligible proportion of the isomeric product of II (resulting from the reverse addition of the alkyllithium[11]). Simultaneous demethylation and bromide formation occurred by the action of boron tribromide in dichloromethane (at −80° to 0°) and 6-(7′-bromoheptyl)salicylic acid (II, R = R′ = H; R″ = Br) was formed. Selective reesterification with ethereal diazomethane gave the phenolic methyl ester[12] which underwent nucleophilic substitution with excess lithium 1-octyne (from *n*-butyllithium and 1-octyne) in tetrahydrofuran–hexamethylphosphoric triamide to give methyl 6-(8′-pentadecynyl)salicylate (II, R = H; R′ = Me; R″ = $C{\equiv}CC_6H_{13}$) having the expected chromatographic (GLC, TLC) and spectroscopic properties (^{1}H NMR, ir).[13] Selective hydrogenation with palladium/barium sulfate in ethyl acetate containing quinoline[14] gave methyl 6-[8′-(*Z*)-pentadecenyl]salicylate identical, chromatographically and spectroscopically, with methyl "anacardate monoene" (II, R = H; R′ = Me; R″ = $CH{=}CHC_6H_{13}$). Hydrolysis with dilute ethanolic potassium hydroxide afforded "anacardic acid monoene[1]" (I, R = H; R′ = $C_{15}H_{29}$), identical with the natural product[15] (^{1}H NMR, ir, GLC, argentation TLC).

Supplementary Material Available. Experimental analysis (6 pages). Ordering information is given on any current masthead page.

References and Notes

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(9) A. A. Durrani and J. H. P. Tyman, *Chem. Ind. (London)*, 762 (1972). 4-Fluoroanisole has given an isomer and 2-fluoroanisole has also given similar substances to H. H. Gilman, W. Langham, and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940), have reported only the isolation of 2-methoxy-5-fluorobenzoic acid (13%) from 4-fluoroanisole and *n*-butyllithium. The trityl ether of 7-chloroheptanol was used in the expectation that the weakly acidic α proton of the acetal would interfere as do the benzylic protons of aromatic acetals. Interaction was not observed.
(10) The proportion of III to II was dependent on the chloro compound:3-fluoroanisole mole ratio. With a mole ratio of 2.245 (%), the proportion of III to II was 3.73, and with a mole ratio of 1.252 (%), it was 1.35. It is believed that RLi formation is proportional to the RCl present. II and III were inseparable by adsorption TLC but readily separable by GLC (230°, SE-52).
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(12) The reported simultaneous methylation of the phenolic group (J. L. Gellerman and H. Schenk) could not be confirmed with ethereal diazomethane at 0°. 3-(7′-Bromoheptyl)phenol was likewise unaffected.
(13) The CO_2Me group was not attacked. The main required product was accompanied by an unidentified impurity with a slightly lower R_f value (TLC) which was separated preparatively.
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A 2,6-Methano-3-benzazocine Related to the Thebaine Diels–Alder Adduct Derivatives

Summary: A novel ring opening of a 1,2,3,4,4a,5,10,10a-octahydro-2,5-methanobenzo[*g*]quinolin-3-yl methyl ketone is the key step of a stereoselective synthesis of a 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine possessing an 11β-$CH_2CH_2C(OH)(CH_3)_2$ fragment.

Sir: The Diels–Alder adduct of thebaine and 3-buten-2-one leads to the most potent analgesics and narcotic antagonists (1) known.[1] A unique structural feature of these molecules is the carbinol functionality at position 7. In view of the clinical utility of pentazocine (2) as an analgesic[2] it was of considerable interest to devise a synthesis of a 2,6-methano-3-benzazocine to which is attached a $-CH_2CH_2C(OH)RR'$ fragment at position 11β (e.g., **9a**).