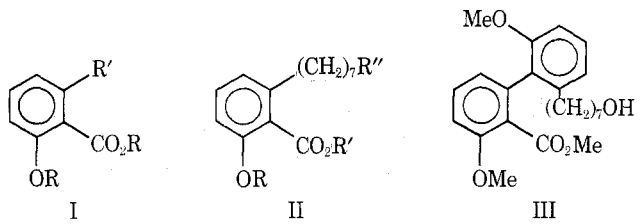
Communications

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.

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(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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(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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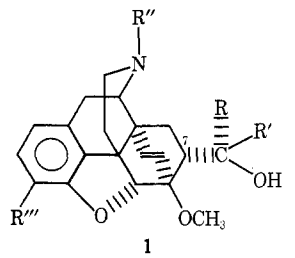
Received June 12, 1975

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**).



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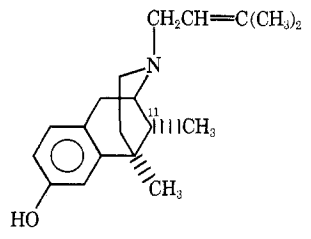


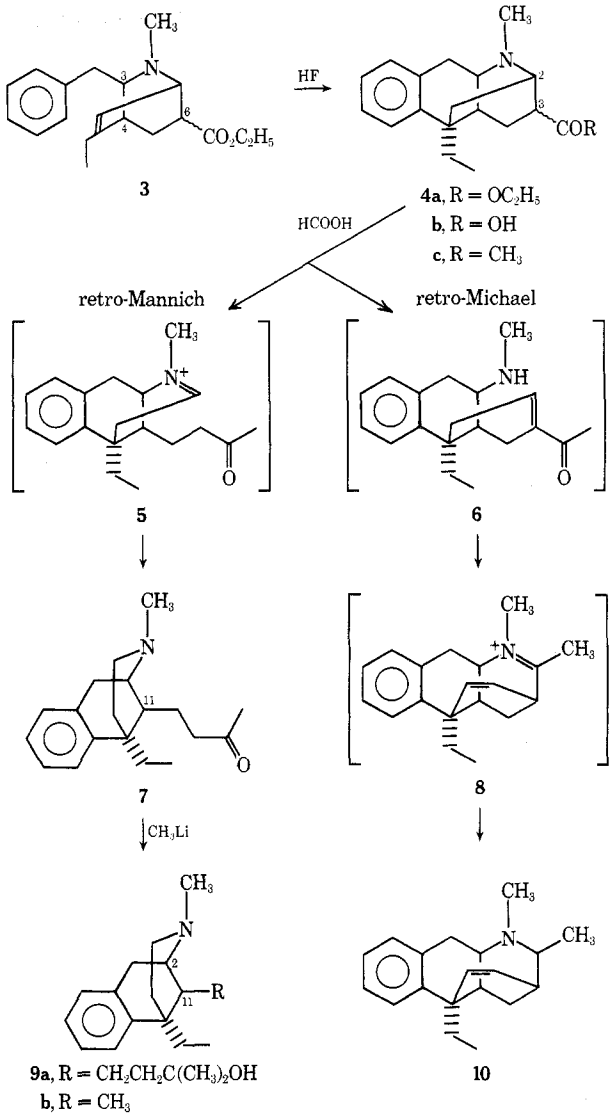
2

Of several reported[3] syntheses of this ring system, the May and Fry extension of the Grewe morphinan synthesis seemed most amenable to modification in order to achieve this goal. Specifically, since 1,2-dihydropyridines have been observed to react with a variety of dienophiles,[4] the 1,2-dihydropyridine obtained from the reaction of 4-ethyl-1-methylpyridinium iodide and benzylmagnesium chloride was treated with ethyl acrylate in refluxing benzene to give ethyl 3-benzyl-8-ethyl-2-methyl-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate (**3**), isolated as its hydrochloride salt in 30% overall yield.[5] The gross structure of **3** was established by a study of the spin decoupled 100-MHz NMR spectrum of the base.[6] The configuration of C-6 in **3** is unimportant in the present context as this carbon will eventually surrender its asymmetry. Note, however, that C-3 and C-4 in **3** possess the same relative configurations as C-2 and C-11, respectively, in **9a**; thus the conversion of **3** → **9a** would constitute a stereospecific synthesis of the latter.

Treatment of **3** with anhydrous HF at room temperature for 24 h gave ethyl 5-ethyl-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-2,5-methanobenzo[*g*]quinoline-3-carboxylate (**4a**), isolated as its hydrochloride salt in 90% yield. Saponification of **4a** to the acid **4b** followed by reaction with CH_3Li/Et_2O gave the ketone **4c**.

Transformation of **4c** to **7** could conceivably be accomplished by an acid-catalyzed retro-Mannich reaction of the β-amino ketone system followed by reduction of the intermediate iminium cation **5**. An analogous transformation ($R_aCONR_bCH_2NR_cR_d \rightarrow R_aCONHR_b + CH_3NR_cR_d$) has been observed using the constant-boiling liquid salt trimethylammonium formate [TMAF, $5HCOOH{\cdot}2N(CH_3)_3$] as the acidic reducing agent.[7] Heating **4c** in TMAF for 15 min at 150–160° gave two compounds which were isolated by fractional crystallization of their hydrochloride salts in yields of 58 and 11%, respectively. The major product was assigned the 3,5-ethenobenzo[*g*]quinoline structure **10** based on its elemental analysis and spectral properties.[8] This compound presumably arises via a retro-Michael reaction of the β-amino ketone system of **4c** to give the intermediate **6**, followed by double-bond isomerization and condensation of the amino and ketone functions to give the intermediate **8**. Finally reduction of **8** gives **10**. This mechanism is speculative since neither of the intermediates **6** or **8** was actually observed.

The minor product was assigned structure **7** based on its elemental analysis and spectral properties,[9] using **9b**[10] as an NMR model compound.[11] Since the retro-Michael reaction leading to **10** presumably required the presence of a



base, experimental conditions free of $(CH_3)_3N$ were sought. It was found that treatment of **4c** with excess formic acid in mesitylene at 115–120° for 24 h increased the yield of **7** to 65%. Finally, **7** reacted with CH_3Li/Et_2O to produce **9a** which was isolated as its CH_3SO_3H salt in 38% yield.

Compounds **7** and **9a** were screened for analgesic activity using the acetyl choline writhing procedure[12] and both were found to be 40% as potent as morphine. The synthesis and analgesic evaluation of several compounds related to **7** and **9a** are in progress and the results will appear in the full paper.

Acknowledgment. We wish to thank Dr. S. D. Clemans for his aid with the spectral data and Mrs. A. K. Pierson for the biological measurements.

Supplementary Material Available. Appendix-Experimental Section (7 pages). Ordering information is given on any current masthead page.

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(9) Spectra: NMR ($CDCl_3$, 60 MHz) δ 7.3–6.8 (4 H), 3.4–2.2 (10 H), 2.2–2.1 (4 H), 2.1–1.5 (4 H), 1.2–0.6 (5 H); ir (KBr, HCl salt) 2930, 2670, 1708, 756, 726 cm^{-1}.
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Received October 7, 1975

Improved Procedures for the Reductive Coupling of Carbonyls to Olefins and for the Reduction of Diols to Olefins

Summary: Active Ti^0 powder is a superior reagent for coupling carbonyls to olefins and for reducing diols to olefins.

Sir: We recently reported that ketones, on treatment with a low-valent titanium reagent prepared from $LiAlH_4$–$TiCl_3$, undergo reductive dimerization to produce coupled olefinic products in high yield.[1] Simultaneously, other workers found that low-valent titanium reagents prepared from Zn–$TiCl_4$[2] or Mg–$TiCl_3$[3] effect similar reductive couplings. Interestingly enough, however, whereas we found that both saturated aliphatic ketones and aromatic ketones couple to olefins, these other workers reported success only with aromatic ketones. Saturated aliphatic ketones were observed to undergo only pinacol dimerization to diols without subsequent deoxygenation. Although others have repeated our reactions,[4] and indeed tetraisopropylethylene, one of the more hindered olefins yet synthesized, has been made by two groups[5,6] using our method, we have nevertheless observed since our publication that the coupling of saturated aliphatic ketones to produce olefins can be erratic. Successful results seem to be dependent on the specific batches of reagents used.

We have expended considerable effort in attempts to overcome this problem, and we now report an improved procedure. We have found that an active Ti^0 metal powder, prepared by Rieke's general method,[7] smoothly couples saturated ketones and aldehydes to olefins. In a representative reaction, $TiCl_3$ (1.54 g, 10.0 mmol) was slurried under nitrogen in 50 ml of dry tetrahydrofuran. Potassium pieces (1.25 g, 32 mmol) were added and the mixture was refluxed for 45 min. Cyclohexanone (0.25 g, 2.5 mmol) was added in 5 ml of THF and the reaction was refluxed 12 hr. After cautious quenching of the reaction with ethanol, filtration through sintered glass and evaporation of solvent provided the coupled olefin in 85% yield. We have repeated this reaction with different batches of $TiCl_3$ from three suppliers and have found it to be reproducible. Some of our results are given in Table I.

Table I. Reductive Coupling of Some Carbonyl Compounds to Olefins with Active Ti^0

$$R_2C{=}O + Ti^0 \rightarrow R_2C{=}CR_2$$

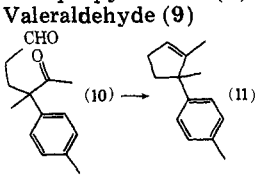
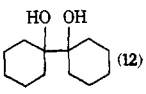
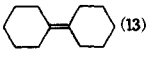
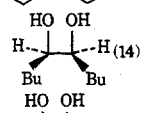
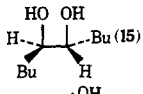
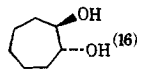
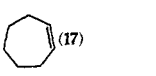
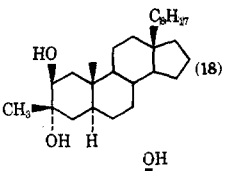
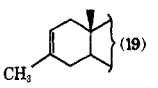
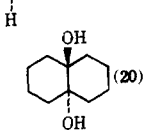
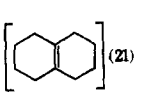
	Isolated olefin yield, %
Cyclopentanone (1)	40
Cyclohexanone (2)	85
Cycloheptanone (3)	86
Cyclooctanone (4)	70
Cyclododecanone (5)	90
Adamantanone (6)	91
Cholestanone (7)	85
Diisopropyl ketone (8)	40
Valeraldehyde (9)	77 (7:3 trans:cis)
 (10) → (11)	55

Table II. Reduction of Some 1,2 Diols to Olefins with Active Ti^0

$$\begin{matrix} HO & OH \\ | & | \\ R_2C & -CR_2 \end{matrix} + Ti^0 \rightarrow R_2C{=}CR_2$$

	Isolated olefin yield, %
 (12) →  (13)	85
 (14) → 5-decene (60:40 trans/cis)	75[a]
 (15) → 5-decene (90:10 trans/cis)	80[a]
 (16) →  (17)	55
 (18) →  (19)	80
 (20) →  (21)	0

[a] VPC yields.

Perhaps the most interesting entries in Table I are the last three. Diisopropyl ketone gives tetraiisopropylethylene (40%) in a yield much higher than that reported[5,6] using $LiAlH_4$–$TiCl_3$ as the coupling agent; so it is clear that quite hindered ketones can be made in acceptable yield. Aldehydes also couple in good yield, but a mixture of double-bond isomers is formed. A control experiment, in which pure *cis*-5-decene was submitted to coupling conditions, indicated that no isomerization of product occurs after the reaction. Intramolecular dicarbonyl coupling to form rings is also possible, although, in the case indicated, the yield is only moderate.

Since pinacol dianions are formed as intermediates in the coupling reaction,[1-3] one would expect Ti^0 to reduce other 1,2 diols to olefins, and we have found this to be the