red absorption (neat) appeared at 3.39 (m), 3.44 (m), 3.52 (m), 6.29 (m), 6.9 (m, broad), 7.10 (s), 7.28 (s), 8.0 (s, broad), 8.51 (s, broad), 9.25 (s, shoulder), 9.53 (s, broad), 11.52 (m), 12.0 (m), and 12.35 (m) μ.

Anal. Calcd for $C_9H_{12}ClO_5PS$ (**12a**): Cl, 11.87; P, 10.37; S, 10.74. Found: Cl, 7.78; P, 10.20; S, 10.48.

Diethyl benzylphosphonate (**11b**, 68.5 g, 0.3 mole) was allowed to react with chlorosulfonic acid (349.5 g, 3.0 mole) in a manner similar to that described for the dimethyl analog **11a** and afforded 80.7 g of crude chlorosulfonated phosphonate **12b**.

Reactions of Chlorosulfonated Dialkyl Benzylphosphonates (12). A. **Pyrolysis.**—A portion (21.6 g, 72 mmoles)[14] of the crude chlorosulfonated dimethyl benzylphosphonate (**12a**) was heated to 150° over a period of 2 hr. Gas evolution commenced at *ca.* 145° and heating of the clear, pale yellow reaction mixture at 150 ± 5° was continued until gas evolution ceased (6 hr). The volatile decomposition product, condensed in a Dry Ice–isopropyl alcohol cooled trap, was identified as methyl chloride by its infrared absorption spectrum.

The amber decomposition residue (18.7 g) solidified to a clear glass on cooling. An aqueous, strongly acidic solution of the residue was neutralized with dilute alkali; distillation to dryness left a cream-colored solid. The solid was allowed to react with excess thionyl chloride (83.5 g, 0.7 mole) at 80° and after distillation of the excess thionyl chloride, the reaction product, an oil, was treated with aniline (49.3 g, 0.53 mole) in refluxing benzene. The cooled reaction mixture was filtered and the filter cake, after washing with water and drying, yielded 27.7 g of a pale tan product **13** melting at 190–210°. Repeated recrystallization of the crude anilide **13** from glacial acetic acid raised the melting point to 242–247°. Infrared absorptions (KBr) occurred at 2.98 (s), 3.0 (s), 6.25 (s), 6.67 (s), 6.76 (s), 7.08 (s), 7.62 (s), 7.7 (s), 7.78 (s), 8.13 (s), 8.23 (s), 8.67 (s), 9.12 (s), 10.61 (s), 10.84 (s), 12.0 (s), 13.3 (s), 13.47 (s), and 14.47 (s) μ.

Anal. Calcd for $C_{25}H_{24}N_3O_3PS$ (**13**): N, 8.80; P, 6.49; S, 6.72. Found: N, 8.76; P, 6.58; S, 6.70.

The crude product **12b** obtained from chlorosulfonation of diethyl benzylphosphonate (**11b**, 25.15 g, 77 mmoles) was also pyrolyzed. Gas evolution started at 159°; after 1 hr at 170 ± 2°, 4.2 ml of a low-boiling liquid condensed in a Dry Ice–isopropyl alcohol cooled trap. An infrared absorption spectrum of the condensate indicated the presence of ethylene and ethyl chloride. The cooled pyrolysis residue (20.7 g), an amber glass, was allowed to react with excess thionyl chloride (95.2 g, 0.8 mole) and then with aniline (55.8 g, 0.6 mole) as previously described to yield 19 g (0.04 mole) of N,N′-diphenyl-*p*-phenylsulfamylbenzylphosphonodiamidate (**13**), identified by melting point and mixture melting point.

B. **Reaction with Aniline.**—Aniline (37.2 g, 0.4 mole) in 50 ml of chloroform was added to a stirred solution of the crude chlorosulfonated dimethyl benzylphosphonate (**12a**, 25.5 g, 85 mmoles) in chloroform (150 ml) at room temperature. After 16 hr at room temperature, the amber-colored reaction mixture containing a white solid was gently refluxed for 5 hr. The cooled reaction mixture was filtered; the filter cake, after washing with fresh chloroform and air drying, was identified as aniline hydrochloride (8 g, 62 mmoles).

Aniline (0.22 mole) was recovered from the combined chloroform filtrate and washings by conventional means. Removal of the chloroform by distillation at about 20 mm (pot temperature <40°) left an oil (21.8 g) that solidified on standing. The solid was recrystallized once from benzene to give 19.2 g (54 mmoles) of **15a** (mp 133–136°). Several recrystallizations from 95% ethyl alcohol raised the melting point to 137.5–139.5°; infrared spectrum (KBr) 3.22 (m), 3.26 (m), 3.29 (m), 3.40 (m), 6.29 (m), 6.70 (m), 7.03 (m), 7.14 (m), 7.5 (s), 7.65 (m), 7.97 (m), 8.12 (s), 8.38 (m), 8.52 (m), 8.58 (s), 9.16 (m), 9.55 (s), 9.83 (s), 10.78 (m), 11.53 (s), 11.84 (m), 12.1 (m), 13.33 (m), 13.7 (m), and 14.5 (m) μ; pmr spectrum (acetone-d_6 solution)[15] τ 6.70 (CH_2P, 2, J_{PCH} = 21.6 cps), 6.38 (CH_3OP, 2, J_{POCH} = 10.5 cps), 2.78 (C_6H_5, c), 2.51 (H_B of C_6H_4 *ortho* to CH_2P, double doublet, J_{AB} = 8.5 cps, $^4J_{PH}$ = 2.1 cps) and 2.2 ppm (H_A of C_6H_4 *ortho* to SO_2, 2, J_{AB} = 8.5 cps).

Anal. Calcd for $C_{15}H_{18}NO_5PS$ (**15a**): C, 50.70; H, 5.10; N, 3.94; P, 8.72; S, 9.02. Found: C, 50.88; H, 4.99; N, 3.86; P, 8.90; S, 9.22.

(14) Based on the assumption that the product is the desired dimethyl *p*-chlorosulfonylbenzylphosphonate (**12a**).

(15) The numbers within the parentheses and preceding the coupling constant refer to the multiplicity of the observed signal (c = complex multiplet).

The crude chlorosulfonated diethyl analog **12b** (26.9 g, 82 mmoles) was treated with aniline (37.2 g, 0.4 mole) in a manner similar to that described above and yielded 22.3 g (58 mmoles) of **15b**, mp 117–118°. Three recrystallizations of **15b** from benzene gave an analytical sample, mp 118–119.5°. Infrared absorptions (KBr) occurred at 3.22 (m), 3.25 (m), 3.28 (m), 3.31 (m), 3.38 (m), 3.46 (m), 6.32 (m), 6.72 (s), 6.79 (m), 7.02 (m), 7.49 (s), 7.63 (m), 8.11 (s), 8.19 (s), 8.63 (s), 9.16 (s), 9.53 (s), 9.81 (s), 10.27 (m), 10.68 (s), 10.8 (m), 11.6 (m), 13.3 (s), 13.61 (m), and 14.53 (m) μ; pmr spectrum (DMSO-d_6 solution) τ 8.90 (CH_3C, ethyl, 3, J_{HH} = 7.0 cps), 6.69 (CH_2P, 2, J_{PCH} = 22 cps), 6.07 (CH_2OP, double quartet, J_{POCH} = 8.1 cps, J_{HH} = 7.0 cps), 2.81 (C_6H_5, c), 2.55 (H_B of C_6H_4 *ortho* to CH_2P double doublet, J_{AB} = 8.2 cps, $^4J_{PH}$ = 2.1 cps), and 2.22 ppm (H_A of C_6H_4 *ortho* to SO_2, 2, J_{AB} = 8.2 cps).

Anal. Calcd for $C_{17}H_{22}NO_5PS$ (**15b**): C, 53.25; H, 5.79; N, 3.65; P, 8.08; S, 8.36. Found: C, 53.36; H, 5.73; N, 3.74; P, 8.10; S, 8.18.

C. **Hydrazinolysis.**—Aqueous 85% hydrazine (7 g, 0.19 mole) was added dropwise in 20 min to a stirred solution of the crude chlorosulfonated dimethyl benzylphosphonate (**12a**, 24.1 g, 81 mmoles) in tetrahydrofuran (100 ml) maintained at 2 ± 4°. After the addition was complete, the reaction mixture was stirred at 0° for 2 hr and filtered to give a white solid (23.8 g after drying). The filtrate, after washing with aqueous saturated sodium chloride and drying over magnesium sulfate, was diluted with petroleum ether (bp 30–60°, 300 ml) and a gummy solid (2.0 g, after drying) precipitated. The combined solid fractions (25.8 g) were washed with portions of cold water until free of chlorine. The dried, aqueous, insoluble reaction product **14a** (17.6 g, 0.06 mole) melted at 128–132° dec. Recrystallization of crude **14a** consecutively from hot water and absolute alcohol raised the melting point to 142–144° dec. Infrared absorptions (KBr) occurred at 2.99 (m), 3.06 (w), 3.18 (m), 3.39 (w), 3.52 (w), 6.32 (w), 7.15 (w), 7.55 (s), 7.58 (m), 7.98 (m), 8.15 (s), 8.35 (m), 8.43 (m), 8.62 (vs), 8.8 (m), 9.15 (m), 9.43 (vs), 9.50 (vs), 11.50 (s), 11.70 (m), and 12.53 (m) μ.

Anal. Calcd for $C_9H_{15}N_2O_5PS$ (**14a**): C, 36.73; H, 5.14; N, 9.52; P, 10.53; S, 10.90; mequiv of Br/g, 13.6. Found: C, 36.85; H, 5.16; N, 9.40; P, 10.49; S, 10.90; mequiv of Br/g, 13.5.

The reaction was repeated with crude chlorosulfonated diethyl benzylphosphonate (**12b**, 29.5 g, 0.09 mole) and aqueous 85% hydrazine (7.2 g, 0.19 mole) and yielded **14b** (18.4 g, 57 mmoles) melting at 126–128° dec. Two recrystallizations from absolute ethyl alcohol provided analytically pure hydrazide **14b** mp (130.5–132° dec); infrared absorption spectrum (KBr) 2.90 (s), 3.03 (m), 3.06 (m), 3.2 (s), 3.37 (m), 3.47 (m), 6.32 (m), 7.15 (m), 7.55 (s), 7.6 (s), 7.97 (s), 8.06 (s), 8.33 (m), 8.58 (vs), 8.82 (m), 9.14 (m), 9.48 (vs), 9.7 (vs), 10.2 (s), 10.3 (s), 11.75 (m), 12.08 (m), 12.68 (m), 14.03 (m), and 14.6 (m, broad) μ.

Anal. Calcd for $C_{11}H_{19}N_2O_5PS$ (**14b**): C, 40.99; H, 5.94; N, 8.69; P, 9.61; S, 9.95; mequiv Br/g, 12.4. Found: C, 40.86; H, 6.10; N, 8.90; P, 9.85; S, 10.04; mequiv Br/g, 12.6.

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Gynocardin

ROBERT A. COBURN AND LOUIS LONG, JR.

Pioneering Research Division, U. S. Army Natick Laboratories, Natick, Massachusetts

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Although gynocardin was first isolated in 1904 by Power and Gornall[1] from the seeds of *Gynocardia odorata*,

(1) F. B. Power and F. H. Gornall, *Proc. Chem. Soc.*, **20**, 137 (1904).

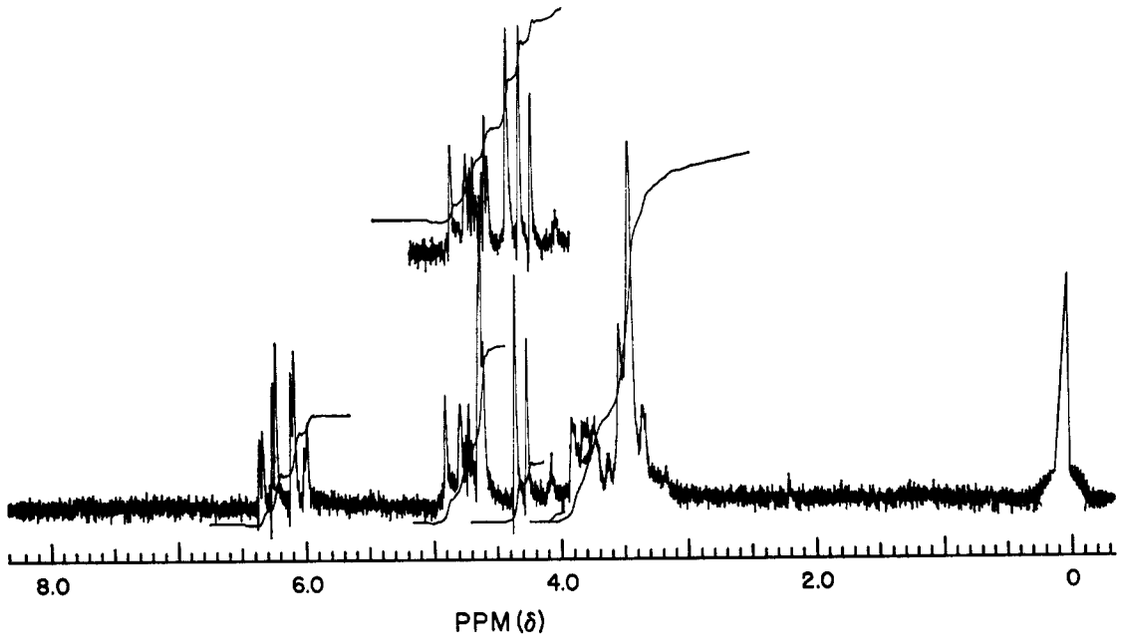


Figure 1.—The nmr spectrum of gynocardin in deuterium oxide (10% solution), with 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard. The lower curve was obtained at 40° and the upper at 50° using a Varian Associates A-60 spectrometer.

R. Br. and later shown to be a cyanogenetic glucoside,[2] the structure of gynocardin has remained unknown.[3] The possibility of an unusual α-glucosidic structure was suggested by the reported large dextrorotatory specific rotation.[2] Recent studies[4] of the biogenetic pathway in cyanogenetic glycoside syntheses indicate that an unusual amino acid precursor may be involved in the biogenesis of gynocardin. We wish to propose a structure of gynocardin based on the evidence presented in this report.

Gynocardin[5] was isolated fron the defatted seeds of *G. odorata*, R. Br., by ethanolic extraction and purified by elution column chromatography on silica gel. The yield of gynocardin was 6.8% of the weight of the fresh seeds. This represents 97% of the calculated quantity of gynocardin contained in the seeds based upon total hydrogen cyanide analysis.[6] The compound and its acetate exhibited physical properties identical with those reported by Power and Lees.[2]

However, elemental analysis indicates the empirical formula $C_{12}H_{17}NO_8$ instead of the previously proposed formula $C_{13}H_{19}NO_9$. Lack of analytical purity in the material obtained by Power and Lees[2] is indicated by their report that gynocardin reduces Fehling's solution, contrary to our observations.

Although no molecular ion is observed in the mass spectral fragmentation pattern of gynocardin,[7] comparison with the spectra of other glucosides[8] suggested that an intense peak (70%) at *m/e* 124 arises from the aglycone. This ion was identified as $C_6H_6NO_2^+$ by exact mass measurement. Homolytic cleavage of a C–O bond β to the nitrile group, producing a glucopyranosyloxy radical and the aglycone ion, would produce this fragment directly from $C_{12}H_{17}NO_8$ but not from $C_{13}H_{19}NO_9$.

Gynocardin exhibits strong absorption at 2.9–3.1 μ (OH), very weak absorption at 4.4 μ (CN), and no absorption in the carbonyl region of the infrared spectrum. The nmr spectrum (Figure 1) of a 10% solution in deuterium oxide showed a doublet (J = 7 cps) at δ 4.85 (one proton), a multiplet at 3.80 (two protons), and a multiplet at 3.50 (four protons), which is consistent with the β-glucoside structure.[9] The two pairs of doublets, centered at δ 6.05 (J = 6.2 cps, J' = 1.0 cps, one proton) and 6.30 (J = 6.2 cps, J'' = 1.4 cps, one proton) are characteristic of vinylic protons and their coupling constant indicates a five-membered ring, unsymmetrically substituted.[10]

The two remaining signals, arising from protons on carbon bearing oxygen (a one-proton multiplet at δ 4.72 and a one-proton doublet at 4.31 with J = 5.3 cps), are coupled to each other and the lower field proton is also coupled to both of the vinylic protons. The magnitude of the coupling between the two nonvinylic protons on the cyclopentene ring indicates that they possess a *trans* configuration.[11] The proposed structure **1** satisfies these requirements and the chemical evidence that follows.

Gynocardin releases hydrogen cyanide upon enzymatic or acid hydrolysis. Treatment with strong base

(2) F. B. Power and F. H. Lees, *J. Chem. Soc.*, **87**, 349 (1905).

(3) A. W. K. DeJong, *Rec. Trav. Chim.*, **28**, 24 (1909); **30**, 220 (1911); C. W. Moore and F. Tutin, *J. Chem. Soc.*, **97**, 1285 (1910); H. C. Brill, *Philippine J. Sci.*, **A12**, 37 (1917).

(4) G. W. Butler and E. E. Conn, *J. Biol. Chem.*, **239**, 1674 (1964); G. W. Butler and B. G. Butler, *Nature*, **187**, 780 (1960); J. E. Gander, *Phytochemistry*, **5**, 125 (1966).

(5) Gynocardin was obtained from the fruit of a living, mature specimen in the permanent collections of the Harold L. Lyon Arboretum of the University of Hawaii. Voucher specimens of this tree, Gillett 1866, are deposited in the herbaria of the Arnold Arboretum of Harvard University, and at the University of Hawaii.

(6) A combined autoenzymatic and acid hydrolysis method was employed. W. O. Winkler, *J. Assoc. Off. Agr. Chemists*, **34**, 541 (1951).

(7) Mass spectra were recorded with an AEI MS-9 high-resolution mass spectrometer using a direct sample insertion technique with a source temperature of 180° (70 ev).

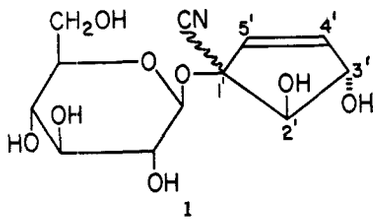
(8) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, Inc., San Francisco, Calif., 1964, p 226.

(9) J. M. van der Veen, *J. Org. Chem.*, **28**, 564 (1963).

(10) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 54.

(11) H. Z. Sable, W. M. Ritchey, and J. E. Nordlander, *Carbohydrate Res.*, **1**, 10 (1965).

liberates ammonia and subsequent acidification produces gynocardinic acid.[2] Power and Lees[2] demonstrated the glucosidic nature of gynocardinic acid by the preparation of phenyl glucosazone from the products of the acid-catalyzed hydrolysis of gynocardinic acid.



1

Catalytic hydrogenation of gynocardin at room temperature and atmospheric pressure results in the uptake of 3 moles of hydrogen when Adams catalyst is used, but only 1 mole when 5% palladium on calcium carbonate is the catalyst.

Gynocardin acetate, earlier reported[2] to be a hepta-acetate, $C_{13}H_{12}NO_2(OAc)_7$, was found to be a hexa-acetate with the revised formula $C_{12}H_{11}NO_2(OAc)_6$ by integration of its nmr spectrum. In a similar fashion, the permethyl derivative of gynocardin was shown to be hexamethyl gynocardin. Hexamethyl gynocardin exhibits a molecular ion peak of low intensity at *m/e* 387 in its mass spectrum.

Acid hydrolysis of gynocardin or gynocardinic acid results in the apparent decomposition of the aglycone moiety as it is released. However, enzymatic hydrolysis of methyl dihydrogynocardinate readily permits the isolation of methyl 1,2,3-trihydroxycyclopentane-1-carboxylate as a colorless oil. This structure was assigned on the basis of its method of preparation and infrared and nmr spectra. Further work to determine the relative configuration at C_1 at this hydroxy ester is in progress.

Experimental Section

Isolation of Gynocardin.—*G. odorata* seeds[5] were removed from their fresh fruit with care to avoid crushing or injuring the seeds. The fresh seeds (50 g) were ground in a food chopper, then stirred in a blender with 200 ml of petroleum ether (bp 40–60°) for 5 min. The resulting slurry was filtered and the residue was washed with hexane. The residue was stirred for 15 min in 200 ml of hot ethanol. This slurry was filtered and the filtrate was concentrated at reduced pressure giving 11.4 g of orange syrup. The syrup was taken up in 95:5 acetone–water and added to 50 g of silica gel (Woelm). The solvent was removed from this mixture at reduced pressure and the mixture was placed on a 500-g column of silica gel (Woelm). Elution with acetone gave 3.4 g of gynocardin as a white solid, mp 163–165°. Recrystallization from isopropyl alcohol gave an analytical sample: mp 165–166°, $[\alpha]^{28}D$ +72.9° (*c* 0.96, water) [lit.[2] mp 162–163°, $[\alpha]^{21}D$ +72.5° (water)].

Anal. Calcd for $C_{13}H_{19}NO_9$: C, 46.83; H, 5.75; N, 4.20. Calcd for $C_{12}H_{17}NO_8$: C, 47.53; H, 5.65; N, 4.62. Found: C, 47.50; H, 5.73; N, 4.47.

Gynocardin Acetate.—Gynocardin (500 mg, 1.65 mmoles) and anhydrous sodium acetate (100 mg) were dissolved in acetic anhydride (20 ml) and the solution was refluxed for 1 hr. The cooled solution was poured into ice water (75 ml) and stirred for 0.5 hr. The resulting white precipitate was collected on a Büchner funnel and recrystallized from ethyl acetate–hexane. There resulted 510 mg of white crystals of gynocardin acetate: mp 119–120°, $[\alpha]^{25}D$ +40.2° (*c* 1.69, chloroform) [lit.[2] mp 118–119°, $[\alpha]D$ +40.4° (chloroform)].

Anal. Calcd for $C_{24}H_{29}NO_{14}$: C, 51.90; H, 5.25; N, 2.53. Found: C, 51.94; H, 5.19; N, 2.48.

No absorption at 2.8–3.1 μ (OH) but strong absorption at 5.73 μ (CO) is exhibited in the infrared. The nmr spectrum (10% deuteriochloroform solution) is similar to that of gynocardin except for an additional signal at δ 2.0, 18 protons, assigned to the 6-methyl group protons.

Hexamethyl Gynocardin.—Gynocardin (300 mg, 1 mmole), methyl iodide (3.0 g, 21 mmoles), and silver oxide (1.7 g, 7.3 mmoles) were added to 5 ml of anhydrous dimethylformamide and the resulting mixture was stirred for 2 days at room temperature. The mixture was filtered and the residue was washed with 3 ml of dimethylformamide. The solvent from the combined filtrate and washing was removed under reduced pressure. The resulting residue was extracted with two 5-ml portions of chloroform. The combined chloroform extract was washed with water and saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure gave 387 mg of colorless oil which was chromatographed on an 80-g column of silica gel (Woelm). Elution with 40:60 ether–chloroform gave 270 mg of colorless oil which was distilled, bp 180° (0.1 mm), to give hexamethyl gynocardin, $[\alpha]^{27}D$ +87.1° (*c* 1.54, chloroform).

Anal. Calcd for $C_{18}H_{29}NO_8$: C, 55.80; H, 7.54; N, 3.62. Found: C, 56.00; H, 7.44; N, 3.76.

No absorption is exhibited in the 2.9–3.1 μ (OH) or the carbonyl region of the infrared.

Methyl Dihydrogynocardinate.—Gynocardin (1.7 g, 5.6 mmoles), barium hydroxide hydrate (3.5 g, 11.2 mmoles), and water (25 ml) were heated on a steam bath for 1 hr. The cooled solution was saturated with carbon dioxide and the resulting precipitate was removed by filtration. Amberlite IR-120 strong acid ion-exchange resin, H^+ form, (20 mequiv) was added and the resulting acidic solution was decanted. This solution was evaporated under reduced pressure leaving 1.5 g (83% yield) of gynocardinic acid as a colorless oil. The oil exhibits broad absorption at 3.4–4.2 μ and strong absorption at 5.84 μ in the infrared, typical of carboxylic acids.

Gynocardinic acid (1.5 g, 4.65 mmoles) in absolute ethanol (20 ml) was hydrogenated at 23° and atmospheric pressure using 10% palladium on charcoal (100 mg) as catalyst. Uptake of hydrogen ceased after approximately 4.6 mmoles of hydrogen was absorbed. The solution was filtered to remove catalyst and an excess of diazomethane in ether solution was added. The resulting solution was warmed briefly to dispel excess diazomethane. Evaporation of solvent gave a white solid which was recrystallized from methanol. There was obtained 1.2 g (76% yield) of methyl dihydrogynocardinate as white crystals: mp 201–203°, $[\alpha]^{25}D$ −24.8° (*c* 1.87, water).

Anal. Calcd for $C_{13}H_{22}O_{10}$: C, 46.16; H, 6.56. Found: C, 46.25; H, 6.72.

Ester carbonyl absorption is evident at 5.78 μ in the infrared. The low-field vinylic proton signals, observed in the nmr spectra of gynocardin and gynocardinic acid, are replaced by a multiplet of four-proton intensity at δ 2.15.

Methyl 1,2,3-Trihydroxycyclopentan-1-carboxylate.—Methyl dihydrogynocardinate (280 mg, 0.83 mmole) was dissolved in 140 ml of aqueous citrate buffer solution (pH 4.5, *ca.* 0.02 *M*), and glucosidase enzyme (prepared from *Penicillium melinii*[12]) was added. The resulting mixture was covered with a toluene layer and maintained at 40° for 24 hr. The mixture was lyophilized and the residue was extracted with 10 ml of acetone. The acetone extract was chromatographed on a 10-g column of silica gel (Woelm). Elution with acetone gave 25 mg of colorless oil which moved as a single spot upon thin layer chromatography in a number of solvent systems. Strong absorption is exhibited at 3.0 (OH) and 5.78 μ (CO) in the infrared. The nmr spectrum (10% solution in chloroform) exhibits a broad multiplet at δ 4.2–4.7 (five protons), a sharp singlet at 3.9 (three protons), and a multiplet at 2.0 (four protons). In the nmr spectrum taken in deuterium oxide the multiplet at δ 4.2–4.7 reduces to a multiplet of only two protons.

Acknowledgment.—The authors wish to express their gratitude to Professor Richard A. Howard of the Arnold Arboretum, Harvard University, for botanical assistance; Dr. George W. Gillett, Director of the Harold L. Lyon Arboretum, University of Hawaii, for a generous sample of *Gynocardia odorata* fruit;

(12) E. T. Reese, F. W. Parrish, and M. Mandels, *Can. J. Microbiol.*, **7**, 309 (1961).

Dr. Gerald O. Dudek, Department of Chemistry, Harvard University, for mass spectral analysis; Dr. Elwyn T. Reese of this laboratory for enzymatic studies; and Mr. Carmine DiPietro of this laboratory for elemental microanalyses.

Phenylation of Monoketones with Diphenyliodonium Chloride[1]

F. MARSHALL BERINGER, WILLIAM J. DANIEL, SUZANNE A. GALTON,[2] AND GERALD RUBIN

The Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, New York 11201

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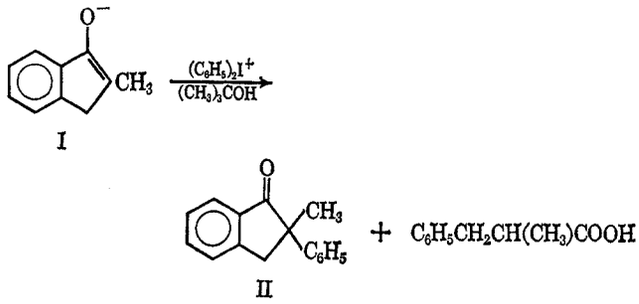
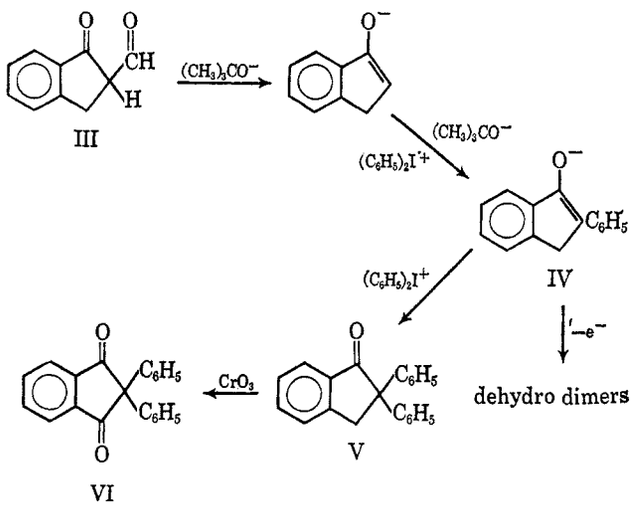
Previous papers from this laboratory have reported on the phenylation of the carbanions of the β-diketones dibenzoylmethane,[3] dimedone,[3,4] and 1,3-indandiones,[5] the triketone tribenzoylmethane,[3] and esters.[6] We have also studied the mesitylation,[7] ethynylation,[8] and vinylation[8] of 2-phenyl-1,3-indandione with iodonium salts. Hauser and co-workers have recently reported on the arylation of a series of β-diketone dicarbanions with diaryliodonium chloride in the presence of sodium amide in liquid ammonia to form γ-phenyl derivatives.[9] The mechanism proposed for the arylations involves ion-pair formation followed by electron transfer from carbanion to iodonium cation with subsequent coupling of the radical pair formed.[5] In the reactions of the dicarbanions it is suggested that coupling occurs between an aryl radical and an anion radical.[9]

In this study we report on the phenylation of the carbanions of a series of monoketones with diphenyliodonium chloride. The results of these phenylations described below can also be interpreted in terms of the previously proposed electron-transfer, radical-pair mechanism for arylation.

The Phenylation of 1-Indanones.—The reaction of 2-methyl-1-indanone (I) with diphenyliodonium chloride in the presence of potassium *t*-butoxide in *t*-butyl alcohol gave the unknown 2-methyl-2-phenyl-1-indanone (II) in 68% yield. There was also formed 20% of α-methylhydrocinnamic acid, a cleavage product of I by potassium *t*-butoxide.



Analogous reaction of 2-formyl-1-indanone (III) gave as the only phenylated product 54% of 2,2-diphenyl-1-indanone (V). In addition 4.5% of 2-(1-keto-2-indanylmethylene)-1-indanone, a known thermal condensation product of III, was obtained. Two other minor products are believed to be dehydrodimers of 2-phenyl-1-indanone (IV). Formation of these products might be explained by decarbonylation of III to 1-indanone, which in the presence of *t*-butoxide gave the monophenyl derivative IV, not isolated but further phenylated to V. It has been reported previously that in the phenylation of 1,3-indandione only the diphenyl derivative was formed.[5] A separate phenylation of IV under similar conditions gave V in 74% yield, plus a small amount of a material also believed to be dehydrodimers of IV. Dehydrodimer formation in the phenylation of the analogous diketone, 2-phenyl-1,3-indandione,



has also been reported;[5] its formation, structure, and reactions have been studied in detail.[10] Compound V was oxidized with chromium trioxide to 2,2-diphenyl-1,3-indandione.[5]

The pmr spectrum of V shows a singlet at τ 6.26 for the methylene protons and a singlet at 2.97 for the phenyl hydrogens in the ratio of 1:5. Ketone IV shows a more complicated spectrum in the region τ 6.32–6.81, owing to the mutual splitting of the methylene and methinyl hydrogens. Absorption at τ 2.98 is attributed to the phenyl protons.

Phenylation of 2-Cyano-1-tetralone (VI).—Reaction of 2-cyano-1-tetralone (VI) with potassium *t*-butoxide and diphenyliodonium chloride in *t*-butyl alcohol gave the previously unknown compound 2-cyano-2-phenyl-1-tetralone (VII) in 50% yield.

(1) This article is taken from the theses of W. J. Daniel and G. Rubin, submitted in partial fulfillment of the requirements for the degree of Master of Science (Chemistry) and in part from the doctoral dissertation of S. A. Galton, submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry). This is publication XXVIII in the series on iodonium salts.

(2) Eastman Kodak Co. Fellow, 1961–1962; Texaco Co. Fellow, 1963; National Institutes of Health, Postdoctoral Fellow, 1963–1965.

(3) F. M. Beringer, P. S. Forgione, and M. D. Yudis, *Tetrahedron*, **8**, 49 (1960).

(4) The phenylation of dimedone has also been reported by O. Neilands, G. Vanags, and F. Gudriniece, *J. Gen. Chem. USSR*, **28**, 1201 (1958); *Chem. Abstr.*, **52**, 19988 (1958); and J. W. Greidanus, W. J. Rebel, and R. B. Sandin, *J. Am. Chem. Soc.*, **84**, 1504 (1962).

(5) F. M. Beringer, S. A. Galton, and S. J. Huang, *ibid.*, **84**, 2819 (1962).

(6) F. M. Beringer and P. S. Forgione, *J. Org. Chem.*, **28**, 714 (1963); *Tetrahedron*, **19**, 739 (1963).

(7) F. M. Beringer and S. A. Galton, *J. Org. Chem.*, **28**, 3417 (1963).

(8) F. M. Beringer and S. A. Galton, *ibid.*, **30**, 1930 (1965).

(9) K. G. Hampton, T. M. Harris, and C. R. Hauser, *ibid.*, **29**, 3511 (1964).

(10) (a) F. M. Beringer, S. A. Galton, and S. J. Huang, *Tetrahedron*, **19**, 809 (1963); (b) F. M. Beringer and S. A. Galton, *J. Org. Chem.*, **28**, 3250 (1963).