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THE REFORMATSKY REACTION ON 1-NAPHTHYL-2-BROMOPHENYL KETONE

THE SYNTHESIS OF 7-(2-BROMOPHENYL)-PERINAPHTENONE*

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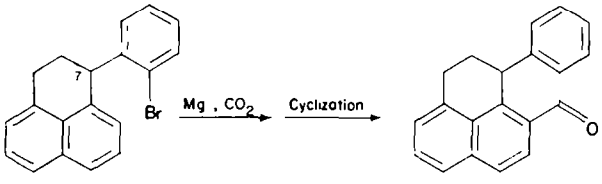
Abstract—The synthesis of 7-(2-bromophenyl)-perinaphthenone (VIII) and 2-bromophenyl-2-naphthyl ketone (IV) is described. Treatment of the *cis*-methyl-β-(2-bromophenyl)-β-(1-naphthyl)-acrylate (VIb) by lithium aluminium hydride under mild conditions unexpectedly led to methyl-β-phenyl-β-(1-naphthyl)-ethylene (XII) by the simultaneous reduction of the nuclear bromine and hydrogenolysis of the oxygen function.

IN A continuation of studies[1] on metabolic products derived from 3,4-benzpyrene, we have had occasion to synthesize C^{14} labeled benzpyrene by the procedure of Heidelberger and Rieke,[2] with some modifications.[3] This procedure involves three steps after the introduction of C^{14} by the Friedel-Crafts acylation of perinaphthane with carbonyl-labeled benzoyl chloride.

The publication of a method of synthesizing C^{14} labeled antracene derivatives, including carcinogenic hydrocarbons such as dibenzantracene, by Catch and Evans,[4] which leads to the polycyclic hydrocarbon in three stages from radioactive carbon dioxide, was of interest to us.

The application of the Catch and Evans' scheme to the synthesis of labeled 3,4-benzpyrene could utilize 7-(2-bromophenyl)-perinaphthane (I), which would then be converted to the corresponding acid through the Grignard, cyclized to the ketonic derivative (II) and reduced with zinc to the desired hydrocarbon. This synthesis has



I II

not been completed, but the results obtained are of some general interest. The present paper describes the preparation of intermediates for (I), and in particular of 7-(2-bromophenyl)-perinaphthenone (VIII). The scheme followed is indicated below.

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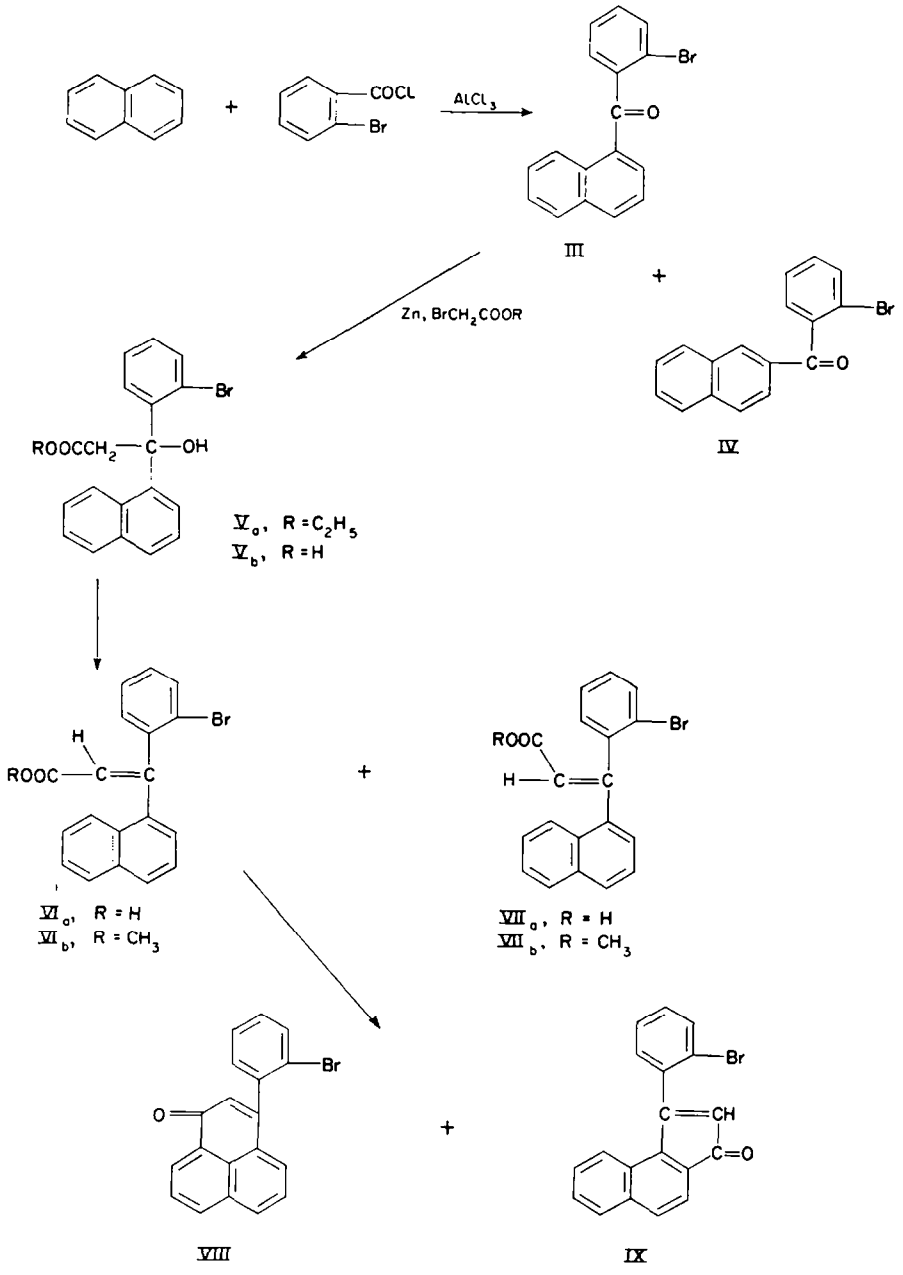
[1] D. S. Tarbell, E. G. Brooker, P. Seifert, A. Vanterpool, C. J. Claus and W. Conway, *Cancer Research* **16**, 1 (1956).

[2] C. Heidelberger and H. S. Rieke, *Cancer Research* **11**, 640 (1951); L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.* **69**, 1658 (1938).

[3] S. C. Pakrashi, *J. Indian Chem. Soc.* **37**, 677 (1960).

[4] J. R. Catch and E. A. Evans, *Chem. & Ind.* (*Rev.*) 78 (1957); *J. Chem. Soc.* 2787, 2790, 2796 (1957).



The Friedel-Crafts acylation of naphthalene by 2-bromobenzoyl chloride was reported[5] to give a ketone, m.p. 89°, which was shown by Bachmann and Chu[6] by an alternative synthesis to be the 1-isomer (III). We have found the usual Friedel-Crafts reaction to give a mixture of the 1- and 2-isomers, (III and IV), in a total yield of

[5] R. J. Knoll and P. Cohn, *Monatsh.* **16**, 207 (1895).
[6] W. E. Bachmann and E. J. H. Chu, *J. Amer. Chem. Soc.* **57**, 1095 (1935).

about 90%; the mixture was separated by a combination of crystallization and chromatography into pure components, and the hitherto undescribed 2-isomer (IV) was obtained as a solid, m.p. 75–76°. The ratio of the 1: 2-isomers in the mixture* was roughly 1.7:1.0.

After many experiments, the yield in the Reformatsky reaction on 2-bromophenyl-1-naphthyl ketone (III) was raised to over 80%. The use of activated zinc[7] or of small excess of zinc with portionwide addition[8] gave unsatisfactory yields. However, by the use of a large excess (fifteen times the theoretical) of freshly fused zinc foil,†,[9] which was added gradually, with five times the theoretical amount of ethyl bromoacetate and of ether–benzene as a solvent,[10] excellent results were obtained.

The crude hydroxy ester (Va) was not isolated and characterized; the corresponding acid (Vb) was prepared in several runs by saponification of the crude ester, and it showed the expected properties.

The crude hydroxy ester was dehydrated by a number of procedures, best by refluxing with acetic anhydride, followed by saponification; the unsaturated product can exist in *cis* and *trans* forms‡ (VI and VII). Both the *cis* and *trans* acids (VIa and VIIa) were obtained crystalline from different dehydration procedures; the *cis* acid was also converted to the crystalline *cis* methyl ester (VIb). The configurations of the two acids were assigned on the basis of cyclization reactions; the acid leading to the crystalline perinaphthenone (VIII) is necessarily the *cis* acid. Recrystallization of the unsaturated acids was accompanied by large losses.

The *cis* ester (VIb) was obtained also by the direct treatment of the hydroxy acid (Vb) with methanolic-hydrogen chloride, followed by chromatography on alumina.

Evidence was obtained for the formation of two cyclic ketones, in addition to the yellow perinaphthenone (VIII), by various cyclization procedures on the hydroxy acid (Vb), on its ester (Va) and on unsaturated acids.

Anhydrous hydrogen fluoride converted the pure *cis* acid (VIa) to a mixture containing about one-third of the crystalline perinaphthenone (VIII), and two-thirds of an isomeric non-crystalline ketone. The crystalline ketone is assigned the perinapthenone structure on the basis of its color and its IR absorption, which shows bands in the carbonyl region only at 1634 and 1613 cm^{-1}. This is reasonable for conjugated aromatic 6-ring ketone such as VIII. The other ketone showed a band at

* The use of the Perrier complex of aluminium chloride and 2-bromobenzoyl chloride gave an even more unsatisfactory mixture, although this procedure with benzoyl chloride and naphthalene gives a good yield of pure 1-ketone (L. F. Fieser, *Experiments in Organic Cheimstry* p. 192. Heath and Co. (1941). Benzoylation of perinaphthane by the Perrier method gives only the 3-benzoyl derivative, which corresponds to the 1-isomer in naphthalene: L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.* **60**, 1658 (1938).

† We are much indebted to Mr. M. Natsume of this laboratory for advice on the Reformatsky reaction.

‡ *Cis* and *trans* designate the relationship of the carboxyl group to the naphthalene nucleus.

[7] L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.* **62**, 576 (1940); C. F. Koelsch and J. A. Anthes *J. Org. Chem.* **6**, 558 (1941).

[8] A. S. Hussey and M. S. Newman, *J. Amer Chem. Soc.* **70**, 3024 (1948); W. E. Bachmann, W. Cole and A. L. Wilds, *ibid.* **62**, 824 (1940).

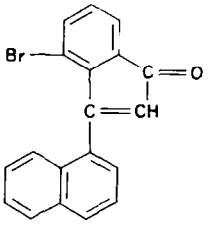
[9] E. Ochiai, T. Okamoto and M. Natsume, *Pharm. Bull., Japan* **5**, 108 (1957); S. Natelson and S. P. Gottfried, *J. Amer. Chem. Soc.* **61**, 970 (1939).

[10] J. Cason and R. J. Fessenden, *J. Org. Chem.* **22**, 1326 (1957); L. H. Klemm and G. M. Bower, *ibid.* **23**, 344 (1958).

1709 cm^{-1}, as well as at 1600 and 1575 cm^{-1}, and hence is probably the conjugated 5-ring ketone (IX), formed by cyclization into the 2- instead of the 8-position of the naphthalene nucleus.

The formation of the two ketones in this cyclization is indicative of the *cis* configuration for VIA, because the *trans* acid (VIIa) could give only a single 5-ring ketone. Furthermore, Fieser and Gates[11] found that hydrogen fluoride cyclization of β-(1-naphthyl)-propionic acid led to both the 6-ring perinaphthenone, and the 5-ring ketone formed by cyclization into the 2-position, analogous to IX. In this case, however, the 6-ring ketone was the predominant product.

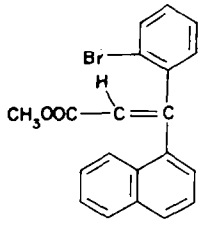
Treatment of the hydroxy acid (Vb) with phosphorous pentoxide in refluxing benzene also yielded the crystalline perinaphthenone, along with another non-crystalline 5-ring ketone, probably X. The crystalline perinaphthenone was also obtained in poor yield by cyclizing the *cis* acid with sulfuric acid.



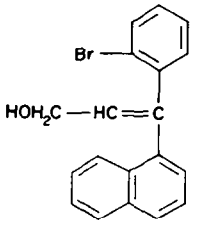
X

Initial attempts to reduce the double bond or the ketone function (or both) in the perinaphthenone (VIII) with sodium borohydride were unpromising;* catalytic reduction with palladium-charcoal of the *cis* acid in methanol at room temperature and ordinary pressure yielded a viscous oil, which was shown by analysis to have lost most of its bromine. We therefore investigated the lithium aluminium hydride reduction of the *cis* methyl ester (VIb), with the expectation of obtaining the allylic alcohol (XI), or the corresponding saturated alcohol, which should be cyclizable to the corresponding perinaphthene or perinaphthane.

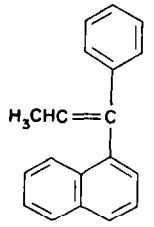
Treatment of VIb with lithium aluminium hydride in tetrahydrofuran at room temperature yielded, instead of the expected alcohol, a bromine-free hydrocarbon,



VIb



XI



XII

* Reduction of perinaphthenone itself with lithium aluminium hydride leads to a complex mixture (V. Boekelheide and C. E. Larrabee, *J. Amer. Chem. Soc.* **72**, 1245 (1950); M. Goldman, *ibid.* **76**, 4032 (1954).

[11] L. F. Fieser and M. D. Gates, Jr., *J. Amer. Chem. Soc.* **62**, 2335 (1940); M. F. Ansell, *J. Chem. Soc.* 575 (1954). has also obtained mixtures of the 5- and 6-ring ketones by cyclization of substituted naphthylpropionic acids.

m.p. 65°, whose analysis indicated the composition, $C_{29}H_{16}$, and whose reactions are in agreement with structure XII.

The complete hydrogenolysis of VIb to a hydrocarbon was unexpected, because, while hydrogenolysis of oxygen functions under more drastic conditions is well known,[12] we have found no analogy to the removal of the oxygen *and* the aromatic halogen under such relatively mild conditions.[13]

The structure XII is based on the analysis, and the formation of acetic acid and benzoic acid as shown by a micro Kuhn-Roth determination.[14] The preparation of a compound, to which structure XII was assigned, has been claimed by an undisclosed procedure.[15]

EXPERIMENTAL*

2-Bromophenyl-1-naphthyl ketone (III) *and 2-bromophenyl-2- naphthyl ketone* (IV). 2-Bromobenzoyl chloride (5 g) prepared[16] in 95% yield (of distilled product) from the acid with thionyl chloride, and naphthlene (3 g) were dissolved in 40 cc carbon disulfide, and 8·5 g aluminium chloride was gradually added with cooling to moderate the vigorous reaction. The reaction mixture was refluxed for 2 hr, cooled and decomposed with ice and 50 cc 6 N HCl; the carbon disulfide and excess of naphthlene were removed by steam distillation. The residue was extracted thoroughly with ether, washed and dried; the solvent was removed and the residual oil distilled in a short path still at 200–210° (0·1 mm), in 90% yield (6·4 g). Crystallization from ethanol gave 4·57 g of a mixture, m.p. 65–72°, which after further crystallization from ethanol yielded 1·93 g *2-bromophenyl-1-naphthyl ketone*, m.p. 89–90°. Repeated chromatography of the residue, using pet ether–benzene (4:1) as eluant yielded additional 1·1 g of the same ketone. The m.p. of this material agrees with that reported for the 1-naphthyl ketone,[5,6] and its elementary analysis for C, H, and Br was in excellent agreement with theory.

The mother liquor after the crystallization of the 4·57 g solid, mentioned above, yielded, on further crystallization, 0·32 g *2-bromophenyl-2-naphthyl ketone* (IV); an additional 1·5 g was obtained by chromatography of the residues from which the 1-isomer had been separated. The analytical sample was prepared by 2 crystallizations from alcohol and 1 from benzene, m.p. 75–76°. (Found: C, 65·68; H, 3·87; Br, 25·80. Calc. for $C_{17}H_{11}BrO$: C, 65·61; H, 3·57; Br, 25·68%).

The reaction carried out with the Perrier complex prepared from 4·5 g 2-bromobenzoyl chloride yielded, by the same separation procedures, a total of 2·24 g of the 1-ketone (III), and 1·87 g of the 2-ketone (IV).

The Reformatsky reaction

Ethyl-β-hydroxy-β-(2-bromophenyl)-β-(1-naphthyl)-propionate (Va) *and the acid* (Vb). To a constantly stirred solution of 2-bromophenyl 1-naphthyl ketone (12·67 g, recovered from an earlier run) in 60 cc of 1:1 benzene–ether under nitrogen was added gradually, with a small crystal of iodine each time, 37 g of freshly fused zinc. Ordinary zinc (20–30 mesh) was melted in a porcelain crucible. The scraps were removed from the top and the shining molten metal was poured on a porcelain plate and immediately pressed with another plate to get thin circular plates of zinc. They were next cut

* All m.p.s. are uncorrected. Microanalyses are by Microtech Laboratories, Skokie, Illinois and Miss A. Smith of this laboratory. Fisher adsorption alumina (neutral) has been used for chromatography unless otherwise stated. Pet ether (b.p. 30-60°) has been used throughout.

[12] L. H. Conover and D. S. Tarbell, *J. Amer. Chem. Soc.* **72,** 3586 (1950), for example.

[13] J. E. Johnson, R. H. Blizzard and H. W. Carhart, *J. Amer. Chem Soc.*, **70,** 3664 (1948); M. Gates and G. Tschudi, *Ibid.* **74,** 1109 (1952); M. Erne and F. Ramirez, *Helv. Chim. Acta* **33,** 912 (1950).

[14] H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta* **38,** 649 (1955); C. F. Garbers, H. Schmid and P. Karrer, *Ibid.* **37,** 1336 (1954); B. Lindquist and T. Storgards, *Acta Chem. Scand.* **7,** 87 (1953). We are thankful to Dr. Olof Cedar of this laboratory for helping in this determination.

[15] E. Luce, *C. R. Acad. Sci., Paris.*, **180,** 145 (1925); the m.p. reported is 55–61°, so it may be impure sample of the hydrocarbon we obtained.

[16] R. Adams and L. H. Ulich, *J. Amer. Chem. Soc.* **42,** 599 (1920).

into small strips and small pieces, and dried *in vacuo* at 100° for 0·5 hr over phosphorous pentoxide before use. Freshly distilled ethyl bromoacetate (20 cc) was added at a rate sufficient to maintain slight refluxing, after the reaction had been initiated by slight warming. The addition took 1·5 hr and refluxing was continued for 4·5 hr longer. The complex was decomposed with acetic acid and water; the ether–benzene layer was separated, the aqueous solution was extracted with benzene, and the combined extracts washed with water and then with ammonia until no more color was removed.

The free *hydroxy acid* (Vb) was obtained by hydrolysis with methanolic base of a Reformatsky product obtained in an earlier run; recrystallization from alcohol and benzene gave the crystalline acid, m.p. 186–186·5° with gas evolution. (Found: C, 62·01; H, 4·24; Br, 21·67. Calc. for $C_{19}H_{15}BrO_3$: C, 61·48; H, 4·08; Br, 21·53%).

cis-*β*-(2-*Bromophenyl*)-*β*-(1-*naphthyl*)-*acrylic acid* (VIa) *and the methyl ester* (VIb). The hydroxy ester prepared above was dehydrated by refluxing for 1 hr with 50 cc acetic anhydride. The product was poured into 250 cc water containing crushed ice, left overnight, and the heavy red oil extracted with ether, washed with 5% sodium carbonate, and with water, and the solvent removed. The crude product was hydrolyzed by refluxing 3 hr with methanolic potash, and 11·32 g (79%) of the crude unsaturated acid was obtained. Recrystallization of the unsaturated acid was always characterized by poor recovery; in this case, two crystallizations from benzene–pet ether gave 3·8 g of cis *acid*, (VIa) in clusters of needles, m.p. 164–165°. The same acid (0·18 g) was also obtained when a benzene solution (8 cc) of 0·2 g of the hydroxy acid (Vb) was refluxed under anhydrous conditions with phosphorous pentoxide (0·1 g) for 3 hr. The analytical sample was prepared from the latter. Found: C, 64·29; H, 3·57; Br, 22·51. Calc. for $C_{19}H_{13}O_2$ Br: C, 64·60; H, 3·71; Br, 22·63%).

The methyl ester (VIb) was prepared by esterification with methanolic hydrogen chloride, and was obtained after chromatography on alumina, short path distillation and recrystallization from methanol, as stout rods, m.p. 110–111°. (Found: C, 65·21; H, 4·02; Br, 22·31. Calc. for $C_{20}H_{15}BrO_2$: C, 65·41; H, 4·12; Br, 21·77%).

The same unsaturated ester was also obtained by methylation of the hydroxy acid (Vb) in the same way, followed by chromatography on alumina.

The trans *acid* (VIIa) was prepared from a Reformatsky run by dehydrating at 200° under water pump suction with a trace of iodine for 15 min followed by saponification with methanolic potash for 2·5 hr.[17] The crude oil was treated with norite in methanol, then was dissolved in benzene–ether and was extracted with 10% sodium bicarbonate. The aqueous alkaline extract was acidified, extracted with ether, the organic layer was washed and dried, and the product crystallized 5 times from benzene–pet ether, m.p. 140–141. (Found: C, 65·00; H, 3·64; Br, 22·98. Calc. for $C_{19}H_{13}BrO_2$: C, 64·60; H, 3·71; Br, 22·63%).

7-(2-*Bromophenyl*)-*perinaphthenone* (VIII)

(a) *By treatment of* *β*-(2-*bromophenyl*)-*β*-(1-*naphthyl*)-*β*-*hydroxy-propionic acid* (Vb) *with phosphorous pentoxide.* A benzene solution (16 cc of 0·37 g (Vb) was refluxed for 3 hr with phosphorous pentoxide. The usual work-up yielded 0·32 g neutral product which was chromatographed over 12 g alumina. A yellow band was eluted with pet ether–benzene (1:1) yielding 0·07 g oil. The IR characteristics, $\nu_{max}^{CHCl_3}$ 1724, (shoulder) 1704 and 1639 cm^{-1}, were typical of a conjugated 5-ring ketone and the product was presumed to be 3-(1-*naphthyl*)-4-*bromo-indene*-1-*one* (X).

A second bright yellow band was eluted with benzene, the 0·03 g oil obtained on removal of the solvent was distilled at 230–240° (10^{-4} mm) and crystallized from ethanol to yield bright yellow hexagonal crystals of 7-(2-bromophenyl)-perinaphenone, m.p. 123–124°.

(b) *By cyclization of* cis-*β*-(2-*bromophenyl*)-*β*-(1-*naphthyl*)-*acrylic acid* (VIa). (i) *with sulfuric acid.* Concentrated sulfuric acid (6 cc) was added to 0·53 g unsaturated acid and the dark solution was left at room temp for 2 hr. A yellow crystalline compound (0·06 g), obtained by the usual procedure, was further purified by chromatography and recrystallizations to afford 0·03 g of the 6-ring ketone (VIII), as the sole product.

(ii) *With anhydrous hydrogen fluoride.* Compound VIa (500 mg) was treated with the equal amount of anhydrous hydrogen fluoride in the usual way.[11] The crude product obtained was chromatographed over alumina. The pet ether–benzene (1:1) eluate yielded 0·3 g oil which from the IR

[17] M. S. Newman, *J. Amer. Chem. Soc.* **62**, 870, 2295 (1940); **64**, 2131 (1942); J. W. Cook, T.Y. Johnson and J. D. Loudon, *J. Chem. Soc.* **537** (1950).

data ($\nu_{max}^{CHCl_3}$ 1724 (Shoulder), 1709, 1600 and 1575 cm^{-1}) appeared also to be a conjugated 5-ring ketone different from the one obtained by the phosphorous pentoxide cyclization of the hydroxy acid (Vb) and was regarded as 1-2-*bromophenyl*)-3-*benz*(e)-*indene*-3-*one* (IX).

The benzene eluate gave 0·14 g 7-(2-*bromophenyl*)-*perinaphthenone*. The analytical sample, m.p. 124–125°, was prepared by two recrystallizations from ethanol. $\nu_{max}^{CHCl_3}$ 1634 (conjugated 6-ring ketone) and 1613 cm^{-1} (conjugated double bond). Found: C, 68·27; H, 3·48; Br, 23·42. Calc. for $C_{19}H_{11}OBr$; C, 68·08; H, 3·31; Br, 23·84%).

Lithium aluminium hydride reduction of cis-*methyl*-β-(2-*bromo*-*phenyl*(-β-(1-*naphthyl acrylate* (VIb) *to methyl*-β-*phenyl*-β-(1-*naphthyl*)-*ethylene* (XII). A solution of the ester, prepared from 7·69 g crude acid (VIa) in 40 cc dry distilled tetrahydrofuran was added dropwise to a suspension of 2·8 g lithium aluminium hydride in 15 cc of the same solvent for 1·5 hr under a stream of nitrogen at room temp; the stirring was continued for additional 0·5 hr. The complex was decomposed with 5 cc ethyl acetate, followed by 15 cc saturated aqueous sodium sulfate and finally the salt itself was added to form a solid crust. The clear solution on decantation and evaporation yielded 4·47 g crude material which was chromatographed directly on alumina. The viscous oil eluted with pet ether–benzene (1:1) solidified on trituration with methanol. On several recrystallizations from the same solvent, white stout rods of *methyl*-β-*phenyl*-β-(1 *naphthyl*)-*ethylene* (XII), m.p. 64–65°, were obtained. The IR spectrum in Nujol showed complete absence of the carbonyl and hydrozyl groups. It exhibited a strong band at 1600 cm^{-1} and a shoulder at 1603 cm^{-1}. λ_{max}^{EtOH} 225, 273, 282, 293 and 312, log ε 4·68, 3·56. 3·72, 3·41 and 2·11; λ_{min}^{EtOH} 245, 276, 290 and 311, log ε 3·16, 3·50, 3·38 and 2·11. (Found: C, 93·28; H, 6·51. Calc, for $C_{19}H_{16}$: C, 93·40; H, 6·60%.

Ozonolysis of the above hydrocarbon did not yield any recognizable product. Micro-hydrogenation was also erratic. Micro Kuhn-Roth determination,[14] however, afforded acetic and benzoic acids, recognized by direct paper chromatographic comparison.