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XV*. THE REACTION OF PHENYLMAGNESIUM BROMIDE WITH 2-NORBORNENE-2-CARBOXYLIC ACID AND METHYL 2-NORBORNENE 2-CARBOXYLATE**

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SUMMARY

2-Norbornene-2-carboxylic acid undergoes almost exclusive conjugate addition of phenylmagnesium bromide to provide a good yield of *exo*-3-phenyl-*endo*- and -*exo*-2-norbornanecarboxylic acids. Methyl 2-norbornene-2-carboxylate reacts with the Grignard reagent in the 1,2-, followed by the 1,4-manner, to yield as the major product *endo*-2-benzoyl-*exo*-3-phenylnorbornane. The structures of these addition products were verified by comparison with independently prepared samples.

RESULTS AND DISCUSSION

The metalation reaction of norbornene with sodium alkyls has been used beneficially for the preparation of norbornyl derivatives by appropriate treatment of the vinylic sodium intermediate, (I). Carbonation affords 2-norbornene-2-carboxylic acid (II)[1], methylation, the 2-methyl derivative[2], and deuterolysis, the labeled olefin[3]. Attempted preparation of the carbinol (III), however, led to the exclusive isolation of rearranged material having structure (IV)[4] (Scheme 1). Before structure (IV) was firmly established for the product of reaction of benzophenone with (I), the possibility that a specimen of (III) could be obtained independently by the addition of phenyl Grignard reagent to the acid (II) was examined. Accordingly, an ethereal solution of phenylmagnesium bromide, in excess of three molar equivalents, was allowed to react with (II). After it had been refluxed for 20 h, the reaction mixture was worked up in a conventional manner to provide, after recrystallization, an acidic product in 68% yield. This product was shown to be a mixture (approximately 2:1)

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* For part XIV, see ref. 8.

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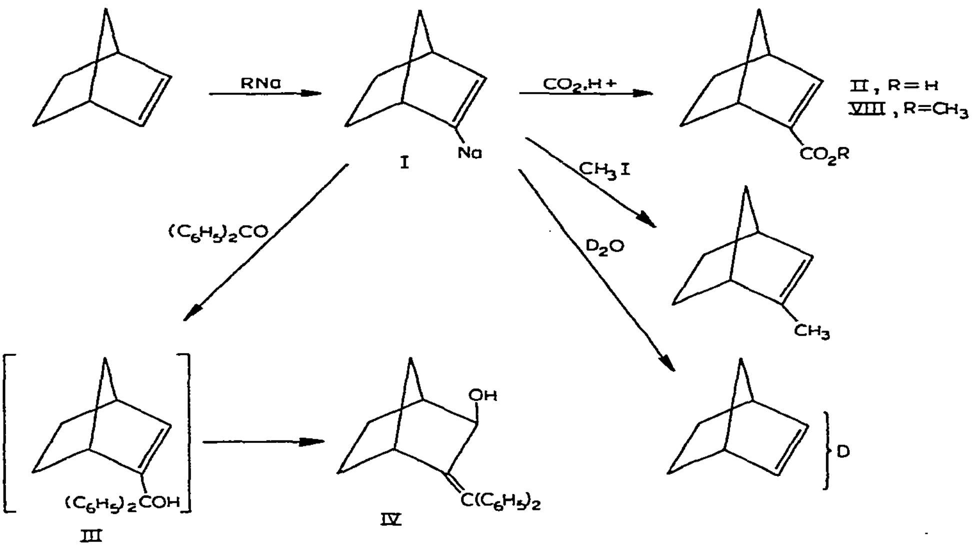
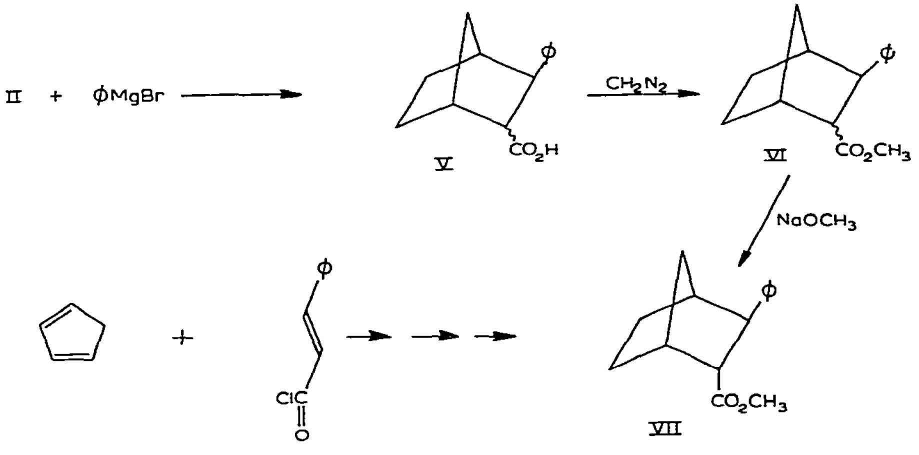


SCHEME 1

of *exo*-3-phenyl-*endo*-3-norbornanecarboxylic acid and *exo*-3-phenyl-*exo*-3-norbornanecarboxylic acid in the following manner (Scheme 2).

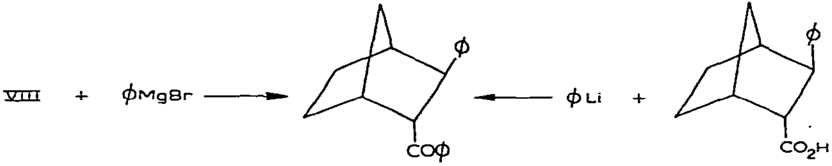


SCHEME 2

Methylation with diazomethane provided, in nearly quantitative yield, a mixture of methyl esters (VI) which showed two peaks on a gas chromatogram. Treatment of (VI) with sodium methoxide in refluxing methanol resulted in the complete conversion of the minor isomer (36.5%) into the major isomer, (VII), whose structure was established by comparison with an authentic sample prepared by the method of Alder, Gunzl, and Wolff[5], and whose stereochemistry had been demonstrated rigorously[5]. Since no attempt was made to determine the isomer ratio in the crude (V), no particular significance should be attached to the *cis*/*trans* ratio observed for the esters (VI). Furthermore, the stereochemistry at C-2 is fixed by the mode of protonation of the magnesium enolate and this is expected to vary with the precise nature of the proton source[6,*]. Of course, the stereochemistry at C-3, exclusively *exo*, reflects the well-known proclivity of norbornenes to undergo *exo* attack at the double bond.

Accompanying the acid (V) was a very small yield of neutral material which exhibited hydroxyl but no carbonyl absorption in the IR. This product proved to be a complex mixture from which no pure substance could be isolated. These results may be contrasted with those of Klein[6] who reported roughly equal amounts of 1,2- and 1,4-addition of phenylmagnesium bromide to 1-cyclohexenecarboxylic acid. The present observation of almost exclusive 1,4-addition is in line with the expected greater reactivity of the strained double bond in (II).

Finally, we report the reaction of phenylmagnesium bromide with methyl 2-norbornene-2-carboxylate (VIII) which produced *endo*-2-benzoyl-*exo*-3-phenylnorbornane (IX), m.p. 95–96.5°, as the major product. Although pure (IX) was obtained in only 15% yield following alumina column chromatography, gas chromatographic analysis indicated that it was formed in the reaction in at least 35% yield. The structure of (IX) was inferred from the presumed *exo* attack of the phenyl group on the intermediate 2-norbornen-2-yl phenyl ketone, coupled with the observation that the ketone could be recovered unchanged after treatment with sodium methoxide indicating that it possesses the more stable *trans* geometry. Additional support for structure (IX) was secured by noting that a ketone having an identical gas chromatographic retention time was produced when phenyllithium was allowed to react with a sample of authentic *exo*-3-phenyl-*endo*-2-norbornanecarboxylic acid:



IX

SCHEME 3

The literature reveals that Nenitzescu and his colleagues[7] prepared a compound, m.p. 93°, having the same constitution as (IX). These workers unaccountable assigned the *endo-cis* geometry to their product. Consideration of their method of preparation (Diels–Alder addition of benzalacetophenone to cyclopentadiene, followed by catalytic reduction) as well as the proximity of melting points, strongly suggests that their ketone is identical with (IX).

EXPERIMENTAL

Reaction of phenylmagnesium bromide with 2-norbornene-2-carboxylic acid (II)

A solution of (II)[1] (1.7 g, 12.3 mmoles) in 10 ml ether was added to a solution of phenylmagnesium bromide made by dilution of 14.8 ml (44.4 moles) of a 3 molar

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[*] In the reaction of phenyl Grignard reagent with cyclohexenecarboxylic acid, Klein[6] observed a change in the stereochemistry of the product when aniline was substituted for sulfuric acid in the protonation step. Analogously, the product (V) exhibited a different isomer ratio when saturated ammonium chloride rather than sulfuric acid was used for hydrolysis of the reaction mixture (See Experimental Part). As no detailed study of this interesting phenomenon was made, it will not be discussed further at this time.

ethereal solution of the Grignard reagent (Arapahoe Chemicals) with 30 ml dry ether. The addition was complete in 20 min and the mixture was maintained at reflux for 11 h before it was poured into ice cold 2 *N* H_2SO_4. The mixture was then extracted several times with ether. The extract was dried and evaporated to give 2.71 g yellow oil which showed a typical broad acid hydroxyl band and an acid carbonyl band in its IR spectrum. The oil was redissolved in ether and extracted with 2 *N* NaOH. After being dried and evaporated, the organic phase afforded a brown residual oil which showed hydroxyl but no carbonyl band in the IR. Attempts to distill or crystallize this oil failed. Chromatography on a thin layer of neutral alumina indicated four poorly resolved components while gas chromatography (20% silicone SF 96 on firebrick, 232°, 125 ml/min) showed at least seven components. Acidification of the alkaline layer liberated the crude acids, (V), which were recrystallized from isohexane to provide 1.81 g (68%) of white crystals, m.p. 79–86.5°.

Methylation with diazomethane of 100 mg of this acid afforded 105 mg of colorless ester (VI) which showed two peaks on a gas chromatogram (20% DEGS on firebrick, 200°, 85 ml/min) in the ratio 36.5 : 63.5. After treatment for 4 h of the ester mixture (VI) with NaOMe in refluxing MeOH solution, followed by reisolation and GLC analysis, it was noted that the minor peak (shorter retention time) had almost completely disappeared and that only the peak corresponding to the major isomer (VII) remained.

When a Grignard reaction mixture from 1 g of acid (II) was hydrolyzed with saturated NH_4Cl prior to acidification with conc. HCl and extraction with ether, there was obtained 483 mg of a white solid* whose melting point, 74–115°, was not sharpened by several recrystallizations from hexane. The IR spectrum of this product was practically indistinguishable from that of the acid mixture, m.p. 79–86.5°, described above. Alder, Gunzl, and Wolff[5] give m.p. 105° for *exo*-3-phenyl-*endo*-2-norbornanecarboxylic acid and m.p. 127.5° for the epimeric *exo-cis* acid.

Methylation with diazomethane of 100 mg of the acid mixture, m.p. 74–115°, produced 109 mg of ester mixture whose gas chromatogram showed the same two peaks as the sample already described. The isomer ratio, however, differed in that the peak with the shorter retention time was now the major (61%) isomer. Sodium methoxide treatment of this mixture of esters, as already outlined for the previous mixture, similarly produced nearly pure (VII). The retention time for samples of (VII) obtained in these experiments was identical with that of the authentic samples of (VII) described below.

Authentic exo-3-phenyl-endo-2-norbornanecarboxylic acid and its methyl ester

Following the literature procedure[5], 16.6 g of *trans*-cinnamoyl chloride was dissolved in 20 g freshly distilled cyclopentadiene and allowed to stand at room temperature for 7 days before it was poured slowly with stirring into a warm (50°) solution of Na_2CO_3 (12 g) in H_2O (150 ml). After being extracted with ether, the aqueous phase was acidified with conc. HCl, saturated with NaCl, and re-extracted several times with ether. This ether layer was dried and concentrated to yield 5.8 g of a yellow oil which crystallized from cyclohexane giving 4 g white crystals, m.p. 90–100°.

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* We thank Mr. Robert S. McNees for carrying out this experiment while in the Department of Chemistry, Ohio State University.

Catalytic hydrogenation of 3.5 g of this product (80 ml EtOH, 100 mg 5% Pd/C) afforded a faintly yellow oil which crystallized on standing. Recrystallization from an ether hexane mixture gave 3.3 g of white crystals, m.p. 90–95°.

Gas chromatography [same conditions as used above for (VI) and (VII)] of the ester mixture (110 mg) obtained by treatment of this acid (110 mg) with diazomethane showed the presence of two components in the ratio 80–90 : 20–10. A more accurate estimation of this ratio was prevented by the closeness of the retention times. The major component (shorter retention time) of this mixture was assigned the structure methyl *exo*-3-phenyl-*endo*-2-norbornanecarboxylate on the basis of Alder's findings[5] that the cycloaddition reaction used here provides a mixture in which the ratio of *trans-endo* acid to *trans-exo* acid is 95 : 5.

Reaction of phenylmagnesium bromide with methyl 2-norbornene-2-carboxylate (VIII)

An ether solution (10 ml) of methyl 2-norbornene-2-carboxylate (VIII) (1.54 g, 10.1 mmoles) was added with stirring over a period of 1 h to a solution of phenylmagnesium bromide (36 mmoles) contained in 42 ml ether which was maintained at 0°. After the addition was complete, the mixture was heated at reflux for 1 h before it was hydrolyzed with saturated NH_4Cl, neutralized with 2 *N* H_2SO_4, and extracted with ether. The ether extract was washed with 2 *N* $NaHCO_3$, H_2O, then dried and evaporated to yield 2.08 g of a viscous yellow oil which showed both hydroxyl and carbonyl (1680 cm^{-1}) absorption in the IR. Chromatography of this oil on 200 g Merck, acid washed, alumina yielded in the isohexane eluates, 415 mg (15% yield) of white, crystalline *endo*-2-benzoyl-*exo*-3-phenylnorbornane (IX), m.p. 93–96°. Recrystallization from an ether/hexane mixture afforded the analytical sample, m.p. 95–96.5°; ν_{max} 1679 cm^{-1}; $\lambda_{max}^{95\%EtOH}$ 245, 280 (sh) mμ, log ε 4.09, 3.25. (Found: C, 86.50; H, 7.59; mol. wt., 278. $C_{20}H_{20}O$ calcd.: C, 86.92; H, 7.29%; mol. wt., 276.)

Continued elution with isohexane and isohexane/ether mixtures provided a series of semi-solid and oily fractions which showed several components on GLC analysis and from which no pure materials were isolated. It was estimated from these analyses that an additional 20% of (IX) was present.

Attempted isomerization of (IX)

A 25 mg sample of (IX) was refluxed in MeOH containing NaOMe for 2 h. The mixture was then allowed to stand for 15 h at room temperature before H_2O was added and it was extracted with ether. From the dried ether extract there was obtained 23 mg of a colorless oil which crystallized from methanol, m.p. 95–96°. A mixed melting point determination with the starting material showed no depresssion.

Reaction of exo-3-phenyl-endo-3-norbornanecarboxylic acid with phenyllithium

A solution in ether (10 ml) of the 3-phenyl-2-norbornanecarboxylic acid (m.p. 90–95°, prepared as outlined above and estimated to consist of 80–90% *trans-endo* acid and 20–10% *trans-exo* acid by analysis of the methyl esters) (432 mg, 2 mmoles) was slowly added to 7.5 ml of an ether solution containing 5 mmoles of phenyllithium. The mixture was refluxed for 2 h before it was cooled, hydrolyzed with 2 *N* H_2SO_4, and extracted with ether. The ether layer was washed with a 2 *N* $NaHCO_3$, H_2O, then dried and evaporated to yield 477 mg of a brown oil. GLC analysis of this product showed that the major constituent (85%) had a retention time identical with that of crystalline (IX) described in the preceding experiments. Furthermore, a mixture of the two substances could not be resolved by lowering the temperature or varying the flow rate. The analysis also showed the presence of several minor constituents and no attempt was made to purify this product.

From the bicarbonate washings, after the appropriate treatment, 28 mg starting acid was recovered.

REFERENCES

1 R. A. Finnegan and R. S. McNees, *J. Org. Chem.*, 29 (1964) 3234.
2 W. F. Erman, *J. Org. Chem.*, 32 (1967) 765.
3 J. E. Franz, C. Osuch and M. W. Dietrich, *J. Org. Chem.*, 29 (1964) 2922.
4 R. A. Finnegan, W. H. Mueller and R. S. McNees, *J. Organometal. Chem.*, 4 (1965) 261.
5 K. Alder, W. Gunzl and K. Wolff, *Chem. Ber.*, 93 (1960) 809.
6 J. Klein, *Tetrahedron*, 20 (1964) 465.
7 E. Cioranescu, A. Bucur, G. Michai, G. Mateescu and C. D. Nenitzescu, *Chem. Ber.*, 95 (1962) 2325.
8 R. A. Finnegan, *Ann. N.Y. Acad. Sci.*, in press.