Treatment with ethanolic picric acid of the nonolefinic material which collected in the first two traps gave no insoluble picrate derivatives characteristic of the tertiary amine III or its *N*-oxide II. From an ethanolic wash of the column itself, however, the picrate derivative of the original amine *N*-oxide II was obtained.

Thermal stability of methylenecyclopropane. A typical sample of olfinic pyrolysate was observed by VPC analysis to be unchanged in composition after standing at room temperature for two weeks. It was observed also, by VPC analysis, that authentic methylenecyclopropane underwent no change when passed through the complete pyrolysis apparatus at 210° as was done with the amine *N*-oxide II.

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Bicyclic Bases. I. 2-Hydroxymethyl-2-phenyl-3-pyrrolidinylmethyl-5-norbornene

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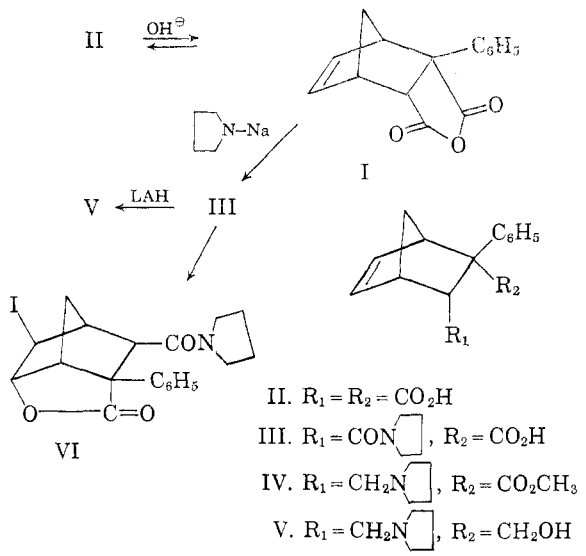
In considering structures that could have analgesic activity, we were attracted to the possibility that compounds such as the norbornene derivatives IV and V might be of interest. In addition to fulfilling the well known structural requirements for analgesic activity,[1] compounds such as IV and V might fit Beckett's proposed "analgesic receptor site"[2] although the "cavity" between the "flat place" and "anionic site" would have to be rather large to accommodate the bulk of the norbornene ring. Some advantage might be gained also by having functional groups fixed in space through their attachment to a rigid bicyclic system which would make any study of the relationship between conformation and pharmacological activity more precise.

Synthesis of these structures was approached through the cyclopentadiene-phenylmaleic anhydride[3] Diels-Alder adduct I. Anhydride I was first prepared by Miller and Mann[4] who characterized their product by saponification to the crystalline dicarboxylic acid II, which was obtained in 51.5% yield. No sterochemical assignment was made to this product. Subsequently, Winternitz, Mousseron, and Rouzier[5] reported that cyclopentadiene and phenylmaleic anhydride reacted to give a noncrystalline product which upon hydrolysis gave 55% of a crystalline mixture of diacids. The French workers concluded on the basis of the isolation of a bromo acid lactone after bromination of their diacid that their crystalline diacid was 70% *cis-exo* and 30% *cis-endo* (II).

In our hands, the reaction of cyclopentadiene and phenylmaleic anhydride under conditions very similar to those reported[4,5] led directly to 69% of pure crystalline *endo*-anhydride I, m.p. 69–70°. We first obtained the crystalline anhydride by saponification of the crude adduct to the pure acid II (66% yield, m.p. 171–172°) followed by cyclization with acetyl chloride to the pure anhydride (87% yield). Proof for the *endo*-configuration of I is given below.



Opening the anhydride ring of I with secondary amines proved to be surprisingly difficult. In 25% aqueous dimethylamine at 55° for many hours as well as in anhydrous dimethylamine in a sealed tube at 60°, I was uneffected and recovered unchanged. The anhydride was also returned in good recovery after heating eighteen hours under reflux in pyrrolidine. However, by dissolving three equivalents of sodium hydride in a large excess of pyrrolidine and allowing the anhydride to stir in the resulting suspension of pyrrolidine salt at room temperature, the desired amide acid was obtained in 87% yield. Structure III is most probable for this product. The *endo*-sterochemistry of the carboxyl group was proved by conversion to an iodolactone VI. This iodolactonization also proves the *endo*-configuration for anhydride function and carboxyl groups of I and II. The position of the amide function in III is inferred from the expected attack of the pyrrolidine amide anion at the less hindered carbonyl group attached to the 3- position of the norbornene ring. Only one sharp-melting amide acid was obtained, indicating definite selectivity. Support for this assignment of the acid and amide functions in III is gained by analogy with the reaction of phenylsuccinic anhydride with ammonia and

(1) N. B. Eddy, *Chemistry & Industry*, 1462 (1959).
(2) A. H. Beckett and A. F. Casy, *J. Pharm. & Pharmacol.*, **6**, 986 (1954).
(3) (a) L. E. Miller, H. B. Staley, and D. J. Mann, *J. Am. Chem. Soc.*, **71**, 374 (1949); see also (b) C. S. Rondesvedt and A. H. Filbey, *J. Org. Chem.*, **19**, 119 (1954), note 2.
(4) L. E. Miller and D. J. Mann, *J. Am. Chem. Soc.*, **72**, 1484 (1950).
(5) F. Winternitz, M. Mousseron, and G. Rouzier, *Bull. soc. chim. France*, 170 (1955).

amines which gives exclusively the succinamic acid with the phenyl and carboxyl group on the same carbon atom.[6] Since the anhydride I is opened in strong alkali to give the *endo-cis* diacid II without any appreciable isomerization to a *trans*-diacid, the *endo*-configuration for the amide group in III is most likely.

The reduction of amide acid III with excess lithium aluminum hydride in tetrahydrofuran led to amino alcohol V in good yield. This basic product was characterized as the fumarate. In pharmacological tests, V showed no analgesic activity.[7] Although in a preliminary experiment, selective reduction of III as the sodium salt in tetrahydrofuran with lithium aluminum hydride to the amino acid followed by esterification with diazomethane to the amino ester IV appeared to proceed in low yield, it was not pursued further due to the lack of analgesic activity for compound V.

EXPERIMENTAL[8]

Phenylmaleic anhydride. Phenylmaleic anhydride was prepared by the method of Miller and Mann.[3a] From 51.7 g. (0.294 mole) of phenylsuccinic anhydride and 105 g. (0.588 mole) of *N*-bromosuccinimide, there was obtained 34.2 g. (67%) of the anhydride, m.p. 121–123°. As reported by Rondesvedt and Filbey,[3b] the use of a nichrome wire stirrer was found to be essential to the success of this reaction.

exo-2-Phenyl-endo-5-norbornene-2,3-dicarboxylic acid anhydride (I). A solution of 34 g. (0.195 mole) of phenylmaleic anhydride and 2.58 g. (0.390 mole) of freshly distilled cyclopentadiene in 150 ml. of benzene was stirred under nitrogen at room temperature for 22 hr. and at 50° for 5 hr. The solvent was removed under reduced pressure on the steam cone. The oily residue crystallized from ether–petroleum ether (b.p. 30–60°).The yield in three crops was 36.2 g. (77%) of anhydride (I) m.p. 65–70°.

From an ether–petroleum ether recrystallization of 0.17 g. of the anhydride (I), m.p. 69–70°, there was obtained 0.09 g., m.p. 69–70°; λ_{max}^{KBr} 5.41, 5.61 μ (anhydride C=O).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.00; H, 5.22.

In the initial experiment, the total noncrystalline product was saponified by the method of Miller and Mann[3a] to give recrystallized II, m.p. 171–172°, in 65% yield. A sample of the diacid II was cyclized to the crystalline anhydride I, m.p. 68–69° by refluxing in acetyl chloride. Thereafter the anhydride I was crystallized directly from the Diels-Alder preparations.

exo-2-Phenyl-endo-3-pyrrolidinecarbonyl-5-norbornene-endo-2-carboxylic acid (III). Thirty-five milliliters of pyrrolidine was reacted with 3.75 g. (0.081 mole) of 53% sodium hydride–mineral oil. The suspension was stirred for 1 hr. at room temperature. A total of 6.50 g. (0.027 mole) of anhydride I was added in portions. The suspension was stirred for 1 hr. and allowed to stand overnight at room temperature. The pyrrolidine was removed under vacuum and the residue was dissolved in water. On acidification, a white solid precipitated which did not dissolve when ether was added. The solid was collected by filtration, washed with water and ether, and air-dried. The crude solid, m.p. 150–151°, was recrystallized from methylene chloride–ether in three crops, all melting at 150–151.5°, totaling 7.29 g. (87%) of amide III.

A recrystallization of 0.25 g. of III, m.p. 150–151.5°, from methylene chloride–ether, gave 0.14 g., m.p. 150.5–151.5°; λ_{max} 5.78 (carboxyl C=O), 6.24 μ (amide C=O).

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.16; H, 6.83; N, 4.44.

Iodolactonization of III *to give* VI. A solution of 0.1 g. of III in 3 ml. of 0.5*N* sodium bicarbonate was combined with a solution of 0.25 g. of iodine and 0.5 g. of potassium iodide in 1.5 ml. of water. The mixture was allowed to stand at room temperature overnight. The dark gummy precipitate was washed with water and dissolved in a mixture of methylene chloride and aqueous sodium thiosulfate. The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. The oily product crystallized from acetone—ether. One recrystallization from acetone—ether gave 0.03 g. of VI, m.p. 222–225°; λ_{max} 5.59, 5.85 (lactone C=O), 6.22 (amide C=O), 6.30 μ (aromatic C=C).

Anal. Calcd. for $C_{19}H_{20}NO_3I$: C, 52.19; H, 4.61; N, 3.20. Found: C, 52.20; H, 4.70; N, 3.41.

1-(endo-2-Hydroxymethyl-exo-2-phenyl-5-norbornene-3-ylmethyl)pyrrolidine (V). A suspension of 7.5 g. (0.198 mole) of lithium aluminum hydride in 250 ml. of dry tetrahydrofuran was stirred at room temperature for 2 hr. and then was heated to reflux and a solution of 15.09 g. (0.0485 mole) of III in 750 ml. of hot tetrahydrofuran was rapidly added. The mixture was heated under reflux for 66 hr. While stirring, the mixture was cooled and carefully decomposed with 22.5 ml. of water. After stirring for 2 hr. the inorganics were removed by filtration and washed with ether. Concentration of the ethereal filtrate gave 12.97 g. of viscous yellow oil, V; $\lambda_{max}^{CHCl_3}$ 3.0 (br., —OH), 6.24, and 6.67 μ (aromatic).

The hydrogen fumarate was prepared from 1.59 g. (0.00563 mole) of V and 0.66 g. (0.00563 mole) of fumaric acid in isopropyl alcohol. The 1.51 g. of fumarate, m.p. 197–200° (67%), was recrystallized from methanol–isopropyl alcohol to give 1.33 g., m.p. 203–205°; λ_{max} 3.0–4.0 (br., carboxyl —OH), 5.90 (carboxyl C=O), 6.08 (C=C), 6.24 (aromatic C=C), 6.32 μ (carboxylate C=O).

Anal. Calcd. for $C_{19}H_{25}NO \cdot C_4H_4O_4$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.30; H, 7.43; N, 3.46.

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(6) R. Anschutz, *Ann.*, **354**, 117 (1907).

(7) We are indebted to W. M. Govier, M.D., and our Department of Pharmacology for these results.

(8) Melting points were determined with a Kofler microhotstage. Infrared spectra were obtained in Nujol mull with a Perkin-Elmer Model 21 Spectrometer unless otherwise noted.

Bicyclic Bases. II. 3-Aminomethyl-2-norbornenearylmethanols

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This note describes an exploratory attempt to find interesting pharmacological activity within a series of basically substituted norbornenearylmethanols.

Our investigation started with the reaction product of *trans*-benzoylacrylic acid and cyclopentadiene which was reported by Winternitz, Mousseron and Rouzier[1] to be a crystalline mixture containing 60% of the *exo-trans*-isomer II and 40% of the *endo-trans*-isomer I. The French workers separated the mixture by a laborious process

(1) F. Winternitz, M. Mousseron, and G. Rouzier, *Bull. soc. chim. France*, 170 (1955).