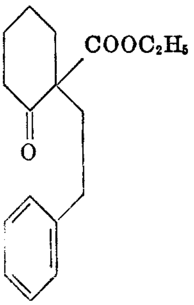
[Contribution from the Indian Association for the Cultivation of Science]

POLYNUCLEAR COMPOUNDS. PART I. A NEW SYNTHESIS OF PYRENE[1]

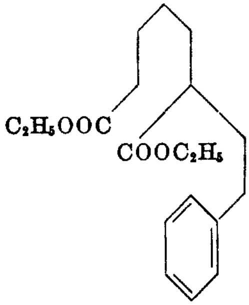
N. N. SAHA and P. BAGCHI

Received June 3, 1955

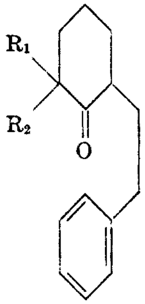
The discovery of the carcinogenic activity of some polynuclear aromatic hydrocarbons has stimulated interest in this class of compounds; particularly the tetracyclic hydrocarbon pyrene assumed new importance with the discovery that 3:4-benzpyrene is one of the most potent carcinogens and is present in coal-tar (1).



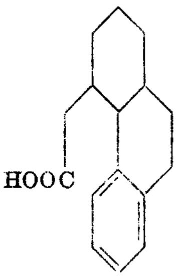
I



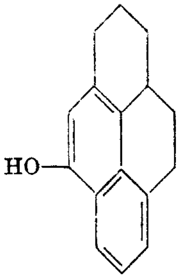
II



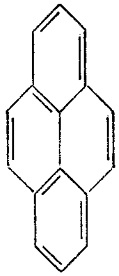
III $R_1 = COOC_2H_5$ $R_2 = H$
IV $R_1 = COOC_2H_5$ $R_2 = CH_2COOC_2H_5$
V $R_1 = H$ $R_2 = CH_2COOH$



VI



VII



VIII

A review of the various methods available for the synthesis of pyrene derivatives (2) would show that at the present moment the only good method is the Cook-Hewett (2e) procedure with the improvements introduced by Bachmann

---

[1] A preliminary communication appeared in *Chemistry & Industry*, 1537 (1954).

and Edgerton (2f) and by Newman (2h). This procedure which employs a tricyclic phenanthrene derivative as the starting material is not suitable for the synthesis of 3:4-benzpyrene. With the object of making pyrene derivatives easily available to those who are engaged in cancer research, a method has been developed for the synthesis of pyrene, which admits of easy extension to that of 3:4-benzpyrene.

The present method, represented below schematically consists in refluxing 2-ethoxycarbonyl-2-β-phenylethylcyclohexanone (I) (3) with a catalytic amount of sodium ethoxide in ethanol when ethyl α-(β'-phenylethyl)pimelate (II) is produced in 66% yield. The ester (II) is invariably found to be contaminated with traces of β-keto-ester represented by (III) as indicated by a ferric chloride test. It has been possible to remove the β-keto-ester completely from II by repeated washing with dilute sodium hydroxide solution. The ester (II) on Dieckmann cyclization with pulverized sodium in benzene under a nitrogen atmosphere furnishes ethyl 2-oxo-3-(β-phenylethyl)cyclohexane-1-carboxylate (III) which cannot be purified by distillation under reduced pressure on account of decomposition. The sodium salt of the Dieckmann product is, therefore, directly refluxed with ethyl bromoacetate to afford ethyl 2-oxo-3-(β-phenylethyl)cyclohexane-1-carboxylate-1-acetate (IV) as a pale yellow viscous liquid. When the ester (IV) is submitted to hydrolysis in a glacial acetic acid—48% hydrobromic acid mixture for 32 hours, a product possessing analytical figures corresponding to a mixture of keto-acid (V) and cyclized acid (VI) is obtained. Light absorption experiments indicate the existence of considerable quantity of a styrene derivative ($\lambda_{\max}^{\text{alc}}$ 262 mμ, log ϵ 1.89). On cyclization by heating the foregoing product with phosphorus pentoxide-phosphoric acid, a crystalline product analyzing correctly for the hexahydropyrenol (VII) is formed in moderate yield. It undergoes smooth dehydrogenation to pyrene (VIII) on treatment with 30% palladium-charcoal at 260° for two hours.

It is interesting to have a comparison of the properties of the product obtained by the present authors with those recorded by the previous workers:

INVESTIGATOR	PYRENE	PICRATE
The Present Authors	Light yellow diamond-like plates, m.p. 149–150°	Deep-red fine needles, m.p. 219–220°
Cook and Hewett (2e)	Colorless leaflets, m.p. 142–144°	Dark-red needles, m.p. 215–218°
Bachmann and Edgerton (2f)	Colorless diamond-shaped leaflets, m.p. 147–148.5°	—
Newman (2h)	M.p. 151.3–151.5° (corr.)	M.p. 225–228° (corr.)

Acknowledgment. We are indebted to the authorities of the Bose Research Institute, Calcutta for allowing us to make light absorption measurements. We are also thankful to Dr. P. C. Dutta for helpful suggestions.

EXPERIMENTAL[2]

2-Ethoxycarbonyl-2-β-phenylethylcyclohexanone (I). To a cooled suspension of powdered potassium (15.1 g., 0.378 g.-atom) in toluene (230 ml.), ethyl cyclohexanone-2-carboxylate

---

[2] All melting points and boiling points are uncorrected.

(66 g., 0.39 mole) was added dropwise with constant shaking. The mixture was kept overnight and the formation of the potassium derivative was completed by refluxing in an oil-bath for one hour more. After cooling, the mixture was treated with phenylethyl bromide (75.7 g., 0.409 mole) and refluxed in an oil-bath for 40 hours. This mixture then was cooled and water was added. The toluene layer was separated and washed with water and dried over sodium sulfate. After removal of the solvent, the residue was distilled under reduced pressure, when the main bulk (51 g., 47.6%) came over at 174–178°/3 mm.

Anal. Calc'd for $C_{17}H_{22}O_3$: C, 74.45; H, 8.02.
Found: C, 74.12; H, 8.3.

Ethyl α-(β'-phenylethyl)pimelate (II). To a solution of sodium ethoxide prepared from sodium (0.21 g., 0.009 g.-atom) and absolute ethanol (25 ml.) was added 2-ethoxycarbonyl-2-β-phenylethylcyclohexanone (24 g., 0.09 mole) and the mixture was refluxed in an oil-bath for three hours. The product was cooled and acidified with glacial acetic acid. After removal of the alcohol under suction, the product was treated with ice-water and extracted with benzene which was thoroughly washed with 5% sodium hydroxide solution to remove acetic acid and a trace of ethyl 2-oxo-3-(β-phenylethyl)cyclohexane-1-carboxylate which was formed during opening of the ring in presence of sodium ethoxide. Finally the benzene solution was washed with water repeatedly until neutral and dried over sodium sulfate. The solvent was removed and the residue was distilled under reduced pressure when a colorless liquid boiling between 186–188°/3 mm. came over, which was redistilled, b.p. 188°/2.5–3 mm. Yield, 18.6 g. (66.4%), n_D^{32} 1.4812.

Anal. Calc'd for $C_{19}H_{28}O_4$: C, 71.25; H, 8.75.
Found: C, 71.79; H, 8.66.

Ethyl 2-oxo-3-(β-phenylethyl)cyclohexane-1-carboxylate (III). Sodium (2 g., 0.087 g.-atom) was powdered under dry xylene and the latter was replaced by dry benzene (70 ml.). Ethyl α-(β'-phenylethyl)pimelate (18 g., 0.056 mole) was added and the mixture was refluxed in an oil-bath for 7½ hours under a nitrogen atmosphere. After the refluxing was over, the product was cooled and acidified with a calculated amount of glacial acetic acid with shaking. Ice and hydrochloric acid then were added and the mixture was extracted with benzene. The benzene layer was separated, washed with water, and finally dried with sodium sulfate. After removal of the solvent the residue was dried under a vacuum. The liquid product thus obtained (14 g.) gave an intense violet color with an alcoholic ferric chloride solution and could not be further purified by distillation under reduced pressure as it decomposed. It was directly used for the next step.

Ethyl 2-oxo-3-(β-phenylethyl)cyclohexane-1-carboxylate-1-acetate (IV). Sodium (2.3 g., 0.1 g.-atom) was finely powdered under dry xylene and the latter was replaced by sodium-dried benzene (150 ml.). To this was added slowly ethyl 2-oxo-3-(β-phenylethyl)cyclohexane-1-carboxylate (27.4 g., 0.1 mole) with constant shaking at room temperature. After allowing it to stand overnight, the mixture was refluxed slowly for two hours in an oil-bath to ensure complete formation of the sodium derivative. The sodio-derivative thus obtained was cooled and treated with ethyl bromoacetate (16.7 g., 0.1 mole) and refluxed for seven hours. After cooling, the product was acidified with glacial acetic acid and slowly treated with ice-water with constant shaking when two layers separated. The benzene layer was removed and the acidic layer was extracted once with ether; the ether extract was combined with the benzene layer, and the combined extracts were washed with water several times and dried with sodium sulfate. After removal of the solvent the residue was distilled under reduced pressure when a lightly colored oil came over at 190–210°/0.4 mm. Yield, 13 g. This on redistillation yielded 11 g. of a pale yellow viscous liquid b.p. 184°/0.2 mm.

Anal. Calc'd for $C_{21}H_{28}O_5$: C, 70.00; H, 7.77.
Found: C, 69.47; H, 8.08.

Hydrolysis of the above ester. Ethyl 2-oxo-3-(β-phenylethyl)cyclohexane-1-carboxylate-1-acetate (10 g.) was treated with a mixture of glacial acetic acid (40 ml.) and 48% hydrobromic acid (50 ml.) and refluxed in an oil-bath for 32 hours. The excess of acetic and hydrobromic acids were removed under suction. The residue after cooling was diluted with water and taken up in ether. The product recovered from the ether was boiled with a solution of sodium carbonate, which then was extracted with ether twice to remove any unhydrolyzed ester. The alkaline layer was then acidified with dilute hydrochloric acid when a semisolid mass separated, which was taken up in ether, washed once with water, and dried with sodium sulfate. After removal of the solvent, the residue was purified by sublimation under reduced pressure when a viscous mass was obtained. This on further distillation gave a slightly colored viscous liquid b.p. 206°/0.4 mm. Yield, 3 g. n_D^{23} 1.5438. λ_{max}^{alc} 262 mμ log ϵ 1.89050.

Anal. Calc'd for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69.
Calc'd for $C_{16}H_{18}O_2$: C, 79.34; H, 7.43.
Found: C, 76.73; H, 7.80.

2-Hydroxy-6,7,7a,8,9,10-hexahydropyrene (VII). The above acid (2.7 g.) was heated at 160–170° for one hour under stirring with a mixture of phosphorus pentoxide (14 g.) and phosphoric acid 89% w/w (11 ml.). The reaction product then was cooled, decomposed with ice-water, and extracted with ether. The ether solution was thoroughly washed with sodium carbonate solution (5%) to remove any uncyclized acid, finally with water until neutral, and then dried with sodium sulfate. After removing the solvent the residue was sublimed at 140–150° (bath temp.) under 0.15 mm. pressure when a yellow crystalline solid was obtained, which was contaminated with some oil. This was crystallized from 95% ethanol in yellow needles, m.p. 129–130°.

Anal. Calc'd for $C_{16}H_{16}O$: C, 85.71; H, 7.14.
Found: C, 85.53; H, 7.03.

Pyrene (VIII). 2-Hydroxy-6,7,7a,8,9,10-hexahydropyrene (0.1 g.) was dehydrogenated with Pd-charcoal 30% (20 mg.) at 260° for two hours. The product was cooled, extracted with ether and dried with sodium sulfate. After removal of the solvent the residue was sublimed under reduced pressure when a light yellow crystalline substance was obtained. This, on further crystallization from absolute ethanol gave light yellow diamond-like plates of m.p. 149–150° sharp.

Anal. Calc'd for $C_{16}H_{10}$: C, 95.05; H, 4.95.
Found: C, 94.70; H, 5.14.

The *picrate* was crystallized from 95% ethanol in deep red fine needles, m.p. 219–220° sharp.

Anal. Calc'd for $C_{22}H_{13}N_3O_7$: N, 9.74. Found: N, 10.00.

SUMMARY

A six-step synthesis of pyrene starting from 2-ethoxycarbonyl-2-(β-phenylethyl)cyclohexanone has been achieved.

JADAVPUR, CALCUTTA 32, INDIA

REFERENCES

(1) COOK, HEWETT, AND HEIGER, *J. Chem. Soc.*, 395 (1933).

(2) (a) WIETZENBOCK, *Monatsh.*, **34**, 193 (1913); (b) FREUND AND FLEISCHER, *Ann.*, **402**, 77 (1914); (c) FLEISCHER AND RETZE, *Ber.*, **55**, 3280 (1922); (d) BRAUN AND RATH, *Ber.*, **61**, 956 (1928); (e) COOK AND HEWETT, *J. Chem. Soc.*, 365 (1934); (f) BACHMANN AND EDGERTON, *J. Am. Chem. Soc.*, **62**, 2970 (1940); (g) CHATTERJE AND BOSE, *J. Indian Chem. Soc.*, **24**, 169 (1947); (h) NEWMAN, *J. Org. Chem.*, **16**, 860 (1951).

(3) BARDHAN AND SENGUPTA, *J. Chem. Soc.*, 2520 (1932).