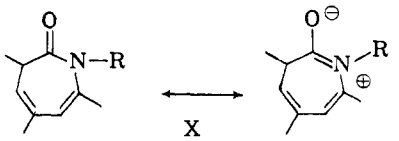
mal conjugated cycloheptadienes[4,5] rather than the anomalous behavior of the 3,5-cycloheptadienones.[5,6] The ultraviolet absorption maximum (252 mμ) of the diene-lactams III and VII is normal and suggests that the diene chromophore can achieve a planar or nearly planar configuration. The correlation of the normal photoisomerization of III and VII with a planar diene chromophore supports the suggestion[5] that the anomalous behavior of 3,5-cycloheptadienones is due to a badly distorted (from planarity) diene chromophore, but it raises the question why the diene chromophore is planar in the diene-lactams III and VII when it is distorted in the 3,5-cycloheptadienones which have a similar disposition of trigonal atoms in the seven-membered ring. The planarity of the diene chromophore in the diene-lactams is probably enforced by the amide group. The steric strain in the planar form is presumably less than the resonance energy of the amide group (X). In a nonplanar structure the resonance



stabilization of the amide group would be lost. The carbonyl stretching frequencies (5.98 and 6.00 μ) of the diene-lactams III and VII are normal showing that interaction of the nitrogen unshared pair with the carbonyl group is not impaired.

The stereoselectivity of the photoisomerization of the diene-lactams III and VII is striking and suggests that steric factors can exert a substantial effect on the course of excited state reactions.

Experimental

2-Aza-1β,4α,6-trimethylbicyclo[3.2.0]hept-6-en-3-one (IV).—A solution of III[7] (3.0 g.) in anhydrous ether (1800 ml.) was flushed with nitrogen and then irradiated with a type A Hanovia mercury arc lamp encased in a water-cooled quartz immersion well. After 1 hr. the 252-mμ maximum characteristic of III had completely disappeared, and the irradiation was stopped. Evaporation of the ether gave a thick, brown residue. The residue was distilled (72–74° at 0.7 mm.) giving crystalline IV. Sublimation (50–80° at 0.005 mm.) of the distillate gave pure IV, m.p. 67–69° (2.1 g., 70%). The product showed no ultraviolet maxima in the 220–360-mμ region.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26; mol. wt., 151. Found: C, 71.26; H, 8.72; N, 9.20; mol. wt. (osmometric), 142.

Hydrogenation of IV.—A solution of IV (1.0 g.) in absolute methanol (30 ml.) absorbed 1 equiv. of hydrogen over 10% palladium-on-carbon catalyst at 25°. Filtration and evaporation of the methanol gave the crude dihydro derivative. Sublimation gave pure 2-aza-1β,4α,6α-trimethylbicyclo[3.2.0]heptane, m.p. 94–95° (0.79 g., 78%).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.54; H, 9.87; N, 9.14. Found: C, 70.29; H, 9.88; N, 8.99.

Pyrolysis of IV.—A solution of IV (0.3 g.) in *n*-hexane (25 ml.) was dropped slowly into a vertical, 6 in. by 0.75 in., Pyrex helices packed pyrolysis column preheated to 430°. The column was swept with oxygen-free nitrogen, and the pyrolysate was collected in a trap immersed in Dry Ice–acetone. After cooling, the column was washed with acetone, and the acetone solution was combined with the pyrolysate. Evaporation of the acetone gave a brown solid. Recrystallization of this solid from aqueous ethanol gave III, m.p. 132–133° (0.15 g., 50%), which was identical in infrared and ultraviolet absorption with authentic III.

Methylation of III.—A solution of III (5.0 g.) and potassium hydroxide (6.50 g.) in acetone (150 ml.) was refluxed gently while methyl iodide (10 g.) was added slowly with stirring. After 15 min. the acetone was evaporated, and water was added to the residue. Extraction with ether, drying, and removal of the ether gave a colorless liquid. Distillation (58° at 0.5 mm.) of the crude product gave pure (vapor phase chromatographic analysis) VII (4.4 g., 80%); λ_{max} 95% EtOH 252 mμ (4540), 6.00 μ (amide carbonyl group).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.79; H, 8.96; N, 8.50.

2-Aza-1β,2,4α,6-tetramethylbicyclo[3.2.0]hept-6-en-3-one (VIII).—A solution of VII (5.0 g.) in anhydrous ether (1800 ml.) was flushed with nitrogen and irradiated with a type A Hanovia mercury arc lamp encased in a water-cooled quartz immersion well. After 1 hr. the 252-mμ absorption characteristic of VII had disappeared, and the irradiation was stopped. Evaporation of the ether and distillation of the product gave VIII (3.5 g., 70%, homogeneous to vapor phase chromatography). This product was identical in infrared and nuclear magnetic resonance absorption and vapor phase chromatographic retention with the major product of the methylation of IV (see below).

Anal. Calcd. for $C_{10}H_{15}NO$ (VIII): C, 72.69; H, 9.15; N, 8.47. Found: C, 72.88; H, 9.33; N, 8.24.

Methylation of IV.—A solution of IV (1.0 g.) and powdered potassium hydroxide (1.3 g.) in acetone (25 ml.) was refluxed gently while methyl iodide (1.4 g.) in acetone (20 ml.) was added slowly with stirring. After 15 min. the acetone was evaporated, and water was added to the residue. Extraction with ether, drying, removal of the ether, and distillation (49–55° at 0.25 mm.) gave a 10:1 (vapor phase chromatographic analysis) mixture of VIII and IX. Preparative scale vapor phase chromatography (15% diethyl succinate on Chromosorb P at 134°) gave the major product VIII and trace amounts of IX. Both products showed infrared carbonyl absorption at 5.93 μ.

Acknowledgment.—The authors are indebted to the National Science Foundation for partial financial support (NSF-G15832) of this research. Ultraviolet spectra were recorded with an instrument made available by a grant (NSF-G14916) from the National Science Foundation. The authors wish to thank Dr. L. A. Paquette for informing them of his results prior to publication.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO., KALAMAZOO, MICH.]

Dihydroazepinone Chemistry. VI. The Photoisomerization of 1,3-Dihydro-3,5,7-trimethyl-2H-azepin-2-one[1]

BY LEO A. PAQUETTE[2]

RECEIVED JULY 29, 1963

The photolysis of 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one (I) has been found to afford a single isomer of 1,4,6-trimethyl-2-azabicyclo[3.2.0]hept-6-en-3-one (II). The structure of this photoisomer has been elucidated from its n.m.r. spectrum. Several transformations of II are described, including its conversion to 1,2,4,6-tetramethyl-2-azabicyclo[3.2.0]heptane hydrochloride (V), a novel bicyclic amine.

In previous papers of this series,[3,4] the one-step ring expansion of sodio 2,6-disubstituted and 2,4,6-trisubstituted phenoxides to the novel 1,3-dihydro-2H-azepin-2-ones by the use of chloramines was discussed. Closer examination of the structure of this class of compounds show them to be heterocyclic 1,3-cycloheptadienes and, as such, they should be capable of photolytic excitation.

(1) Part V: L. A. Paquette, *Tetrahedron Letters*, **No. 29**, 2027 (1963).

(2) Department of Chemistry, The Ohio State University, Columbus 10, Ohio.

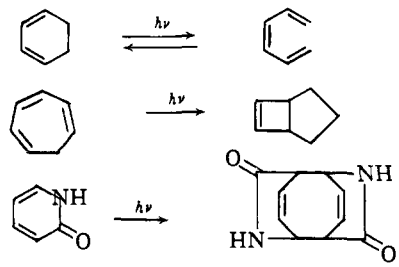
(3) L. A. Paquette, *J. Am. Chem. Soc.*, **84**, 4987 (1962).

(4) L. A. Paquette, *ibid.*, **85**, 3288 (1963).

The photoisomerization of 1,3-cycloheptadienes has recently enjoyed much success. For example, colchicine,[5] dihydrothujic acids,[6] γ-tropolone methyl ether,[7] eucarvone,[8] and various other substituted 1,3-cycloheptadienes,[9] and cycloheptatriene[9a] are some of the systems which have been studied to date and which have been shown to give rise to bicyclic systems possessing a cyclobutene ring. The failure of 3,5-cycloheptadienones to photoisomerize has, however, been noted[9c,10]; a different course is followed whereby carbon monoxide is liberated and a mixture of geometric isomers of 1,3,5-hexatriene results.

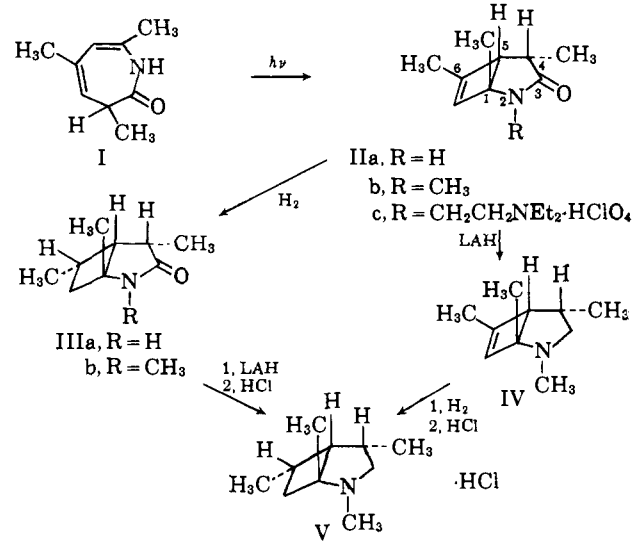
Despite the fact that photochemical isomerizations of 1,3-cycloheptadienes have been well documented and have attained a degree of sophistication and reliability sufficient to enable the method to be appropriate for aiding in structure proof,[6] investigations of suitable heterocyclic analogs in light-induced reactions have been very limited. In this regard, Fonken[11] has reported the ready photoisomerization of the oxygen heterocycle, muconic anhydride, and Paquette[1] has demonstrated the light-induced isomerization of 2,3-dihydro-1,3,5,7-tetramethyl-1H-azepine, a cyclic dienamine.

The present paper reports our studies of the photolysis of 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one (I).[12] This investigation was of theoretical interest for at least two reasons. First, although compound I cannot be converted to its carbonyl-conjugated isomer under conditions of very strong basic treatment,[13] it is conceivable that this process could occur initially under the conditions of photolytic excitation before proceeding to photoproduct. Secondly, and perhaps of greater significance, I bears the same formal resemblance to 2-pyridone that 1,3-cycloheptadiene does to 1,3-cyclohexadiene.[1,3] Cyclohexadiene, on irradiation, is converted into 1,3,5-hexatriene; this ring cleavage reaction is the preferred photochemical reaction of this structural type.[14] Cycloheptadiene follows the normal reaction course characteristic of rings that contain $(2n + 3)$ members and n conjugated double bonds and on photolysis affords Δ^6-bicyclo[3.2.0]heptene.[9b,c] On the other hand, 2-pyridone affords an exception to the normal behavior of six-membered conjugated rings. This heterocyclic system undergoes light-induced



dimerization to 3,7-diazatricyclo[4.2.2.$2^{2,5}$]dodeca-9,11-diene-4,8-dione.[15-17] The irradiation of I was therefore studied to determine if the type of "abnormal reactivity" observed with 2-pyridone would appear in the seven-membered ring counterpart.

Irradiation of I in tetrahydrofuran (or methanol) solution with an unfiltered 200-w. Hanovia lamp for 48 hr. at room temperature gave a single crystalline photoisomer, readily separable from starting material I by column chromatography on Florisil,[18] in 77.5%



yield (based on recovered I). The recovered dihydroazepinone could be reirradiated repeatedly and excellent total yields obtained. In agreement with structure IIa, this photoisomer exhibited infrared peaks (in Nujol) at 3180 (secondary amide N–H), 1690 (γ-lactam carbonyl), 3070 and 1640 cm.$^{-1}$ (*cis*-substituted double bond in strained ring). The ultraviolet spectrum showed only terminal end absorption. The n.m.r. spectrum[19] was fully compatible with the proposed structure; a low field complex doublet at 366 c.p.s. (J = 1.5 c.p.s.) was assigned to the cyclobutene proton and a complex multiplet centered at 161 c.p.s. to the proton at 4, the pattern suggesting splitting with an adjacent methyl group and proton. In addition, the absorption peaks of the various methyl groups were located at 116 (triplet, J = 1.5 c.p.s., 6-methyl), at 8 (singlet, 1-methyl), and at 73 c.p.s. (doublet, J = 7 c.p.s., 4-methyl). Finally, the hydrogen at position 5 gave rise to a doublet (with additional small splitting) centered at 185.5 c.p.s. (J = 10 c.p.s.). Because the coupling constant of protons on adjacent carbon atoms is a function of the dihedral angle between the two C–H planes, the large observed J-value for the 5-hydrogen can be accommodated only by angles of 0 or 180° with the proton at 4.[20] Examination of models suggests that a *cis* arrangement of protons at positions 4 and 5 (see structure II) affords a dihedral angle of ap-

(5) O. L. Chapman, H. G. Smith, and R. W. King, *J. Am. Chem. Soc.*, **85**, 803, 806 (1963); E. J. Forbes, *J. Chem. Soc.*, 3864 (1955).

(6) D. J. Pasto, *J. Org. Chem.*, **27**, 2786 (1962).

(7) O. L. Chapman and D. J. Pasto, *J. Am. Chem. Soc.*, **80**, 6685 (1958); **82**, 3642 (1960).

(8) G. Büchi and E. M. Burgess, *ibid.*, **82**, 4333 (1960); J. J. Hurst and G. W. Whitman, *Proc. Chem. Soc.*, 116 (1961).

(9) (a) W. G. Dauben and R. L. Cargill, *Tetrahedron*, **12**, 186 (1961); (b) O. L. Chapman and D. J. Pasto, *Chem. Ind.* (London), 53 (1961); (c) O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Am. Chem. Soc.*, **84**, 1220 (1962); (d) J. Rigaudy and P. Courtot, *Tetrahedron Letters*, **No. 3**, 95 (1961).

(10) O. L. Chapman and G. W. Borden, *J. Org. Chem.*, **26**, 4185 (1961).

(11) G. J. Fonken, *Chem. Ind.* (London), 1575 (1961).

(12) A brief discussion of some of our results in this area can be found in ref. 1.

(13) The N-methyl derivative of I was recovered unchanged after prolonged treatment with the methylsulfinyl carbanion: L. A. Paquette, *J. Org. Chem.*, **28**, 3590 (1963).

(14) D. H. R. Barton, *Helv. Chim. Acta*, **42**, 2604 (1959).

(15) L. A. Paquette and G. Slomp, *J. Am. Chem. Soc.*, **85**, 765 (1963); G. Slomp, F. A. MacKellar, and L. A. Paquette, *ibid.*, **83**, 4472 (1961).

(16) E. C. Taylor and R. O. Kan, *ibid.*, **85**, 776 (1963); E. C. Taylor, R. O. Kan, and W. W. Paudler, *ibid.*, **83**, 4484 (1961).

(17) W. A. Ayer, R. Hayatsu, P. deMayo, S. T. Reid, and J. B. Stothers, *Tetrahedron Letters*, **No. 18**, 648 (1961).

(18) Florisil is a magnesia–silica gel adsorbent manufactured by the Floridin Co., Tallahassee, Fla.

(19) Spectra were obtained in deuteriochloroform with a Varian 4300-2 spectrometer operating at 60 Mc. or with a Varian A-60 spectrometer (TMS = 0 c.p.s.). The author is indebted to G. Slomp and his staff for these spectra.

(20) For further discussions of this topic, see R. W. Lenz and J. P. Heeschen, *J. Polymer Sci.*, **51**, 247 (1961); K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4626 (1961); M. Karplus and D. H. Anderson, *J. Chem. Phys.*, **30**, 6 (1959); M. Karplus, *ibid.*, **30**, 11 (1959), and leading references cited in these papers.

proximately 0°, while a *trans* arrangement produced an angle of about 109°. *Such a strong coupling of the protons in question is therefore possible only in that conformation which gives rise to the 0° dihedral angle, namely, the cis isomer II.*

These results indicate that the dihydroazepinone I does in fact isomerize "normally" under photolytic conditions and, at least in this sense, is not a formal homolog of 2-pyridone. Furthermore, the reaction represents a very facile two-step synthetic entry (starting with the appropriate phenols) into the otherwise difficultly accessible 2-azabicyclo[3.2.0]heptene system.

When IIa was heated to 60° with sodium hydride in dimethylformamide, followed after cooling, by the addition of excess methyl iodide, there resulted a 70% yield of the N-methyl derivative IIb. Again, the spectral data were in full agreement with this formulation; in the n.m.r., the spectrum was similar to that of IIa, but with the addition of the N-methyl resonance line at 165 c.p.s. Although inversion of configuration at C-4 could be ruled out on this basis, this possibility was considered highly unlikely *a priori* because of the energetically unfavorable severe 1,3-interactions which would result between the methyl groups at C-1 and C-4. A similar reaction with 2-diethylaminoethyl chloride afforded the N-diethylaminoethyl derivative as its crystalline perchlorate IIc in 83% yield.

Catalytic hydrogenation of IIa at atmospheric pressure proceeded readily with the uptake of one mole of hydrogen to give the single isomer IIIa, thereby confirming by chemical means the bicyclic nature of the photoproduct. The 6-methyl group in IIIa was assigned the stereochemistry indicated, solely on the basis of the steric factors which were likely operative when IIa approached the catalyst surface.[21]

Lithium aluminum hydride reduction of IIb gave rise to the unsaturated bicyclic amine IV which was characterized as its picrate. Hydrogenation of IV and conversion of the product to its crystalline hydrochloride gave the bicyclic amine hydrochloride V. This material was also prepared by the catalytic reduction of IIb, followed by lithium aluminum hydride reduction of the resulting IIIb. The two samples of V were found to be identical by the usual criteria.

Experimental[22]

1,4,6-Trimethyl-2-azabicyclo[3.2.0]hept-6-en-3-one (IIa). A. Irradiation in Tetrahydrofuran.—A solution of 45.4 g. (0.30 mole) of 1,3-dihydro-3,5,7-trimethyl-2H-azepin-2-one (I) in 450 ml. of purified tetrahydrofuran was irradiated with an immersion type Hanovia unfiltered 200-w. lamp for 48 hr. at room temperature. The solution was concentrated and the residual oil was chromatographed on a Florisil[18] column. Elution with hexane afforded 15.6 g. of recovered I, m.p. 131–133°, while elution with acetone–hexane (1:10) gave 23.1 g. (77.5% yield based on recovered I) of a white solid, m.p. 69–71°. Recrystallization of this material from hexane gave pure photoisomer IIa, m.p. 72–73°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26; mol. wt., 151. Found: C, 71.25; H, 8.36; N, 9.20; mol. wt. (cryoscopically in $CHCl_3$), 158.

B. Irradiation in Methanol.—A solution of 5.0 g. (0.033 mole) of I in 350 ml. of methanol was irradiated with an immersion type Hanovia unfiltered 200-w. lamp for 22 hr. at room temperature. The solution was concentrated and the brown oil was chromatographed on a Florisil[18] column. Elution with hexane afforded 1.15 g. of recovered I, m.p. 129–132°, while elution with acetone–hexane (1:10) gave 2.10 g. (54.5% yield based on recovered I) of a white solid, m.p. 70–72°. Recrystallization of this material from hexane gave pure photoisomer IIa, m.p. 72–73°, identical in all respects with the above material.

1,2,4,6-Tetramethyl-2-azabicyclo[3.2.0]hept-6-en-3-one (IIb).—A mixture of 5.0 g. (0.033 mole) of IIa and 1.55 g. of 51.5% sodium hydride–oil dispersion (0.033 mole) in 40 ml. of dimethylformamide was warmed to 50° during 0.5 hr. with stirring. After cooling, 4.9 g. (0.036 mole) of methyl iodide was added to the brown solution in one portion and a precipitate immediately formed with a simultaneous color change to pale yellow. After warming at 50° for 0.5 hr., the mixture was cooled, ether (50 ml.) was added, and the inorganic solid was separated by filtration. The filtrate was evaporated and the residual oil and distilled to give 3.8 g. (69.8%) of colorless liquid, b.p. 100–110° (11 mm.), $n^{26}D$ 1.4835. Redistillation of this material gave pure IIb, b.p. 110–111° (11 mm.), $n^{25}D$ 1.4830.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.47; H, 8.94; N, 8.22.

2-Diethylaminoethyl-1,4,6-trimethyl-2-azabicyclo[3.2.0]-hept-6-en-3-one Perchlorate (IIc).—A mixture of 5.0 g. (0.033 mole) of IIa and 1.55 g. (0.033 mole) of 51.5% sodium hydride–oil dispersion in 40 ml. of dimethylformamide was warmed to 50° during 0.5 hr. with stirring. After cooling, 4.9 g. (0.036 mole) of diethylaminoethyl chloride in 11.4 ml. of xylene solution was added in one portion and the brown mixture was warmed to 50° for 1 hr. The contents were cooled, ether (50 ml.) was added, and the inorganic solid was separated by filtration. The filtrate was evaporated and the residual oil was distilled to give 6.85 g. (83.2%) of pale yellow oil, b.p. 101–110° (0.20 mm.), $n^{26}D$ 1.4806. This material was converted to its perchlorate in the usual manner. After recrystallization of the salt from ethanol–ether, IIc was obtained as a white solid m.p. 102–104°.

Anal. Calcd. for $C_{15}H_{26}ClN_2O_5$: C, 51.49; H, 7.49; N, 8.01. Found: C, 51.19; H, 7.54; N, 7.70.

1,4,6-Trimethyl-2-azabicyclo[3.2.0]heptan-3-one (IIIa).—A solution of 9.2 g. (0.061 mole) of IIa in 100 ml. of ethanol containing 200 mg. of 10% palladium-on-charcoal was hydrogenated at atmospheric pressure and room temperature. The hydrogenation stopped after the uptake of 96% of theory. The solvent was removed under reduced pressure and the crystalline residue was slurried in hexane, cooled, and filtered to give 7.7 g. (82.8%) of grayish white blades, m.p. 94.5–96°. Two recrystallizations of the crude product from hexane gave pure IIIa as colorless prisms, m.p. 97.5–98.0°.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H 9.87; N, 9.14. Found: C, 70.78; H, 9.93; N, 9.33.

1,2,4,6-Tetramethyl-2-azabicyclo[3.2.0]hept-6-ene (IV).—To a stirred slurry of 1.06 g. (0.028 mole) of lithium aluminum hydride in 40 ml. of anhydrous ether was added dropwise a solution of 4.0 g. (0.0242 mole) of IIb in 10 ml. of ether. When the addition was completed, the mixture was refluxed with stirring for 2 hr. With ice cooling, the mixture was treated with 1 ml. of water, 1 ml. of 25% sodium hydroxide solution, and 3 ml. of water, in that order. The precipitated inorganic salts were removed by filtration and washed well with ether The combined filtrates were evaporated and the resulting colorless oil was treated directly with ethanolic picric acid to give 4.65 g. (50.5%) of yellow picrate, m.p. 212–213°. Pure picrate was obtained from ethanol as yellow prisms, m.p. 212–213°.

Anal. Calcd. for $C_{16}H_{20}N_4O_7$: C 50.52; H, 5.30; N, 14.73. Found: C, 50.55; H, 5.53; N, 14.69.

A sample of the picrate was reconverted to the base in the usual manner to give after distillation, a colorless liquid, b.p. 61° (11 mm.), $n^{25}D$ 1.4560.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.34. Found: C, 79.18; H, 11.30.

1,2,4,6-Tetramethyl-2-azabicyclo[3.2.0]heptane Hydrochloride (V). A. Hydrogenation of IV.—A solution of 2.0 g. (0.0132 mole) of the IV in 50 ml. of ethanol containing 200 mg. of platinum oxide was hydrogenated at atmospheric temperature and pressure. The uptake of hydrogen ceased after the consumption of 1 mole. The catalyst was separated by filtration and the filtrate was treated with a slight excess of ethereal hydrogen chloride and evaporated under reduced pressure. The residual oil was treated with a small amount of ether and allowed to stand overnight in a refrigerator (5°). The crystalline product was separated by filtration and dried to give 1.4 g. (56.0%) of white solid, m.p 205–208°. Pure hydrochloride was obtained as a white solid from ethanol–ether; m.p 213.5–215°.

Anal. Calcd for $C_{10}H_{20}ClN$: C, 63.30; H, 10.63; N, 7.38. Found: C, 63.70; H, 10.46; N, 7.41.

B. From IIb *via* IIIb.—A solution of 7.0 g. (0.0424 mole) of IIb in 100 ml. of absolute ethanol containing 200 mg. of 10% palladium-on-charcoal was hydrogenated at atmospheric temperature and pressure. The uptake of hydrogen stopped after

(21) Although in the hydrogenation of bent bicyclic systems the convex or open side is usually considered to be less hindered, the effect in IIa and IV of the angular 1-methyl group (which decreases the ease of approach from the convex side) and of the nitrogen atom at position 2 (which may exert some sort of stereoelectronic control) remains ambiguous. The stereochemical assignments III and V (6-position only) are therefore at best only speculative, but appear most likely because of analogies in the existing literature.

(22) Melting points are corrected. The author is indebted to Dr. D. R. Myers and his associates of the Physical and Analytical Chemistry Department of The Upjohn Co. for the analytical and spectral data.

the consumption of 1 mole (99.6% of theory). The catalyst was removed by filtration and the filtrate was evaporated. Benzene (50 ml.) was added and evaporated to remove remaining traces of ethanol. The residual oil was used directly without further purification.

To a stirred slurry of 1.9 g. (0.05 mole) of lithium aluminum hydride in 75 ml. of anhydrous ether was slowly added a solution of the hydrogenation product IIIb in 25 ml. of ether. The mixture was refluxed with stirring for 2 hr., cooled, and decomposed by the addition of 2 ml. of water, 2 ml. of 25% sodium hydroxide, and 6 ml. of water in that order. The precipitated aluminate salts were separated by filtration and the filtrate was treated directly with ethereal hydrogen chloride. The precipitated hydrochloride was filtered, washed with ether, and dried. There was obtained 7.3 g. (90.9% for the two steps) of white solid, m.p. 204–205°. Pure V was obtained as a white solid from ethanol–ether; m.p. 213.5–215°. This material was identical in all respects with that prepared in part A.

Acknowledgment.—The author is deeply indebted to Paul E. Marlatt for the preparation of sufficient quantities of I to enable this work to be carried out.

[CONTRIBUTION FROM THE EVANS CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY, COLUMBUS 10, OHIO]

The Synthesis and Ionization Constants of the Six Hydroxybenzo[c]phenanthrenes[1]

BY MELVIN S. NEWMAN AND JOCHANAN BLUM[2]

RECEIVED SEPTEMBER 4, 1963

The syntheses of the six hydroxybenzo[c]phenanthrenes is described. None of these compounds exists to any detectable extent in an isomeric ketonic form. 1-Hydroxybenzo[c]phenanthrene is appreciably weaker as an acid than the other five isomers.

The compound benzo[c]phenanthrene (I) and certain of its derivatives have been of interest to us in several connections. Originally, the attempt to correlate the carcinogenic activity of I and of the six monomethyl derivatives of I with some property of the hydrocarbons was of major concern.[3] More recently, interest in the properties of the functional derivatives of I has been of concern because of the steric strains inherent in this polycyclic system.[4] For example, all six of the monocarboxylic acids have been prepared and their ionization constants determined.[5]

In the present study, all of the hydroxy derivatives of benzo[c]phenanthrene have been prepared with three objectives in mind: a, to measure the ionization constants; b, to see if any of these compounds might exist partly or totally as an isomeric ketone; and c, to supply compounds for testing of carcinogenic or anticarcinogenic activity.

The ionization constants have been measured and are listed in Table I together with those of a few related compounds.[6] The most noteworthy facts are that 4-phenanthrol and 1-benzo[c]phenanthrol are appreciably weaker in acid strength than all of the other phenanthrols and benzo[c]phenanthrols. We attribute this to steric hindrance to solvation of the corresponding anions. A similar explanation for the weakness of hindered aliphatic acids has been advanced.[7]

No evidence of a ketonic component has been obtained in any member of this series[8] as judged by the absence of a carbonyl absorption band in the infrared spectra.

The compounds have been sent for testing[9] in the cancer field to Dr. James A. Miller, McArdle Memorial Laboratory, Madison, Wis. More of each compound is available if there are other persons interested in other measurements.

TABLE I

IONIZATION CONSTANTS OF PHENANTHROLS AND BENZO[c]-PHENANTHROLS (50% BY WEIGHT ETHANOL)

	pK_a
2-Phenanthrol	10.50
4-Phenanthrol	11.33
9-Phenanthrol	10.51
Hydroxybenzo[c]phenanthrene	
1-	11.31
2-	10.44
3-	10.35
4-	10.56
5-	10.54
6-	10.26

The syntheses of 1-, 2-, and 3-hydroxybenzo[c]-phenanthrene were accomplished by demethylation of the corresponding methoxy benzo[c]phenanthrenes, which were synthesized[10] as shown in the accompanying formulas. Both 2-methoxy and 2-hydroxybenzo[c]-phenanthrene[11] and 3-methoxybenzo[c]phenanthrene[12] have been prepared.

The demethylation of the 2-methoxy and 3-methoxy compounds was accomplished without difficulty, but the demethylation of 1-methoxybenzo[c]phenanthrene

(1) This work was supported by a grant from the National Institutes of Health.

(2) Postdoctoral Fellow, 1963.

(3) In this connection the following papers are of interest: (a) K. H. Takemura, M. D. Cameron, and M. S. Newman, *J. Am. Chem. Soc.*, **75**, 3280 (1953); (b) M. S. Newman, M. Levy, and M. Szwarc, *ibid.*, **77**, 4225 (1955); (c) M. S. Newman and S. Otsuka, *J. Natl. Cancer Inst.*, **21**, 721 (1958).

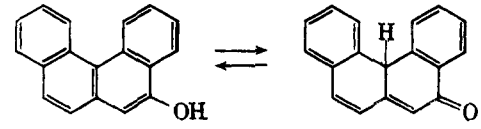
(4) The study of the geometry of I and related compounds by X-ray crystallography has been under investigation: see F. H. Herbstein and G. M. J. Schmidt, *J. Chem. Soc.*, 3302 (1954); F. L. Hirshfeld, S. Sandler, and G. M. J. Schmidt, *ibid.*, 2108 (1963).

(5) M. S. Newman and H. Boden, *J. Am. Chem. Soc.*, **83**, 115 (1961).

(6) In a private communication, Dr. W. N. White and Mr. H. Rosenberg report that the ionization constants of 2-, 3-, and 9-phenanthrol, 1- and 2-naphthol, and 1- and 2-anthrol in 50% aqueous methanol have pK_a values of 10.02 to 10.22.

(7) G. S. Hammond and D. H. Hogle, *J. Am. Chem. Soc.*, **77**, 338 (1955); M. S. Newman and T. Fukunaga, *ibid.*, **85**, 1176 (1963).

(8) It was thought that perhaps isomerization to a ketonic state would relieve part of the steric strain; *e.g.*



(9) Hydroxybenzo[c]phenanthrenes may be of interest as possible metabolic products of the parent hydrocarbon. For references to polycyclic aromatic hydrocarbon metabolites and their possible connection with cancer, see A. Pullman and B. Pullman, *Advan. Cancer Res.*, **3**, 117 (1955); E. Boyland and P. Sims, *Biochem. J.*, **84**, 571 (1962), and references therein. No work in this connection has been carried out with benzo[c]phenantbrene to our knowledge.

(10) See M. S. Newman and R. M. Wise, *J. Am. Chem. Soc.*, **78**, 450 (1956), and M. S. Newman and M. Wolf, *ibid.*, **74**, 3225 (1952), for analogous syntheses.

(11) (a) A. L. Wilds and R. G. Werth, *J. Org. Chem.*, **17**, 1154 (1952); (b) J. Szmuszkovicz and E. J. Modest, *J. Am. Chem. Soc.*, **72**, 566 (1950); (c) G. T. Tatevosyan and V. O. Babayan, *Zh. Obshchei Khim.*, **22**, 1421 (1952).

(12) J. Szmuszkovicz and E. J. Modest, *J. Am. Chem. Soc.*, **70**, 2542 (1948).