B. From Cyclization of Acid.—A mixture of 0.5 g. of 2-(1-naphthylmethyl)-1-naphthoic acid, prepared by carbonating the Grignard reagent of 1, 30 ml. of glacial acetic acid, and 15 ml. of 48% hydrobromic acid was treated as has been described above under A, and the product was isolated similarly. Dibenz[*a,h*]-anthracene was obtained: m.p. 259–262°, 0.18 g. (40%).

10a,10b-Dihydrobenzo[*e*]naphtho[1,2-*b*]pyrene (5).—A mixture of 0.5 g. of 7-phenyldibenz[*a,h*]anthracene, 1.0 g. of $AlCl_3$, 0.5 g. of selenium powder, and 50 ml. of dry benzene was heated under reflux for 15 min. The reaction mixture was cooled and the complex mixture was decomposed with dilute hydrochloric acid and extracted with benzene. The benzene solution was concentrated and chromatographed on neutral alumina.[20] The first band, a colorless blue fluorescent band, was discarded. The second band, a yellow green fluorescent band, was collected and the solvent was removed giving orange needles, m.p. 186–187°, 0.25 g. (50%), of 5.

Anal. Calcd. for $C_{23}H_{18}$: C, 94.88; H, 5.12. Found: C, 94.39; H, 5.31.

The wave length maxima for 5 are λ 325, 285, and 252 mμ.

TNF Adduct of 5.—The adduct was prepared by mixing hot benzene–ethanol solutions of 5 and TNF. The product was obtained as fine black needles, m.p. 232–233°, from benzene–ethanol.

Anal. Calcd. for $C_{41}H_{23}N_3O_7$: C, 73.52; H, 3.47; N, 6.28. Found: C, 73.16; H, 3.86; N, 6.84.

Benzo[*e*]naphtho[1,2-*b*]pyrene (6).—A mixture of 0.50 g. of 5, 0.50 g. of DDQ,[15] and 35 ml. of dry benzene was heated under reflux for 20 hr. The solution was cooled and diluted with 150 ml. of benzene. The solution was washed with 10% NaOH and then with water, dried over $MgSO_4$, and concentrated. The concentrate was chromatographed on alumina.[20] The third band (reddish orange) which was eluted from the column was collected and gave red needles, m.p. 265–267°, 0.35 g. (70%). The analytical sample, m.p. 266–267°, was prepared by first subliming the material *in vacuo* and then recrystallizing the sublimate from benzene–ethanol.

Anal. Calcd. for $C_{28}H_{16}$: C, 95.42; H, 4.58. Found*: C, 95.32; H, 4.42.

The wave length maxima for 6 are λ 390 336, 319, 307, 275, and 263 mμ.

TNF Adduct of 6.—This adduct was prepared essentially as was the adduct of 5, m.p. 275–276°.

Anal. Calcd. for $C_{41}H_{21}N_3O_7$: C, 73.76; H, 3.17; N, 6.29. Found*: C, 73.79; H, 3.33; N, 5.79.

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The Formation and Rearrangement of 8a-Amino-4a,5,6,7,8,8a-hexahydro-4H-1-benzopyrans

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The reaction of enamines derived from alicyclic ketones with acrolein to give bicyclic amino ketones was first reported by Stork and Landesman.[1] The versatility of the reaction and its use in the synthesis of medium-size rings was studied in detail by Untch,[2] but only a limited investigation of the possible reaction intermediates was described.

Our interest in N-phenylpiperazyl Mannich bases as potential analgetic agents led us to synthesize a series of 2-(4-phenyl-1-piperazyl)bicycloalkanones (Table II). This report is concerned with the isolation and rearrangement of aminohexahydrobenzopyran intermediates (Table I) formed in the reaction of certain enamines with α,β-unsaturated carbonyl compounds.

The reaction of acrolein with 1-(1-cyclohexen-1-yl)-4-phenylpiperazine in dry benzene at 10° resulted in the formation of a crystalline compound, m.p. 117–118°. The elemental analysis indicated that addition of acrolein to the enamine had taken place. The infrared spectrum ($CHCl_3$) showed no carbonyl band, but a sharp band of medium intensity was present at 1660 cm.$^{-1}$. This suggested that we were dealing with the aminohexahydrobenzopyran derivative I. Confirmatory evidence for this structure was provided by the n.m.r. spectrum ($CDCl_3$) which showed resonance peaks at τ = 3.87 (doublet) and 5.41 (multiplet) p.p.m. due to the 2- and 3-protons of the dihydropyran nucleus. An analogous addition reaction occurs with aldehyde enamines and α,β-unsaturated aldehydes.[3] As expected, compound I is very unstable in the presence of acid; immediate and practically quantitative decomposition to N-phenylpiperazine hydrochloride and 3-(2-oxocyclohexyl)propionaldehyde[4] occurs upon treatment with dilute hydrochloric acid at 0°.

The formation of aminohexahydrobenzopyran derivatives seems to be general for the reaction of cyclohexanone enamines with acrolein. We found that in the case of the previously reported 2-morpholinobicyclo[3.3.1]nonan-9-one,[1] the aminohexahydrobenzopyran was the precursor. After a solution of acrolein and 4-(1-cyclohexen-1-yl)morpholine in dry benzene had been allowed to stand at room temperature for a few hours, the solvent was removed *in vacuo* to give a liquid whose infrared spectrum showed the typical enol ether band at 1660 cm.$^{-1}$. Vacuum distillation converted this material into the bicyclic amino ketone.

That the stereochemical requirements for formation of aminohexahydrobenzopyran intermediates are quite stringent was shown by the fact that 1-(1-cyclopenten-1-yl)-4-phenylpiperazine and 1-(1-cyclohepten-1-yl)-4-phenylpiperazine on reaction with acrolein gave the bicyclic amino ketones VI and VII (Table II) directly. Furthermore, when 1-(1-cyclohexen-1-yl)-4-phenylpiperazine was allowed to react with cinnamaldehyde, no intermediate was isolated; the bicyclic amino ketone VIII was obtained in good yield from benzene solution.

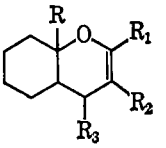
When compound I was heated in dimethylformamide–triethylamine solution, a mixture of isomeric bicyclic amino ketones (II and III) was formed in 84% yield. The infrared spectrum now exhibited a strong ketone carbonyl band at 1710 cm.$^{-1}$; the band at 1660 cm.$^{-1}$ in compound I was absent. Unequivocal proof of structure for II was obtained by degradation to 4-cyclooctene-1-carboxylic acid and formation of the known carboxamide.[1] An attempt was made to degrade compound III by this method, but no cyclooctenecarboxylic acid could be detected.

Results obtained from column and thin layer chromatography indicated that the bicyclic amino ketone mixture consisted of at least 75% II, m.p. 129–130°. Compound III, m.p. 100–101°, could be isolated in yields ranging from 5 to 20%. The stereochemistry

(1) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5129 (1956).
(2) Karl G. Untch, Ph.D. Thesis, Columbia University, 1959; Microfilm 60-1163, University Microfilms, Inc., Ann Arbor, Mich.
(3) G. Opitz and I. Löschmann, *Angew. Chem.*, **72**, 523 (1960).
(4) J. Colonge, J. Dreux, and M. Thiers, *Bull. soc. chim. France*, 370 (1959).

TABLE I

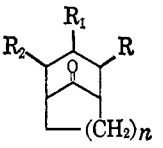
AMINOHEXAHYDRO-4H-1-BENZOPYRANS



Compd.	R	R_1	R_2	R_3	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
I	4-Phenyl-1-piperazyl	H	H	H	71	117–118	$C_{19}H_{26}N_2O$	76.51	8.72	9.40	76.34	8.66	9.49
IV	4-Phenyl-1-piperazyl	H	CH_3	H	43	126–127	$C_{20}H_{28}N_2O$	76.92	8.97	8.97	76.58	8.92	8.95
IX	4-Phenyl-1-piperazyl	C_6H_5	H	C_6H_5	44	129–130	$C_{31}H_{34}N_2O$	82.66	7.56	6.22	82.47	7.34	6.23
XII	Morpholino	C_6H_5	H	H	72	102–103	$C_{19}H_{25}NO_2$	76.25	8.36	4.68	75.95	8.06	4.85
XIII	4-Phenyl-1-piperazyl	C_6H_5	H	H	75	96–97	$C_{25}H_{30}N_2O$			7.49			7.40

TABLE II

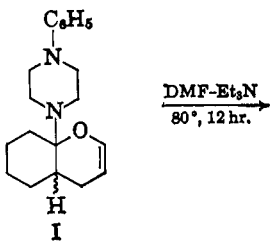
2-AMINOBICYCLOALKANONES



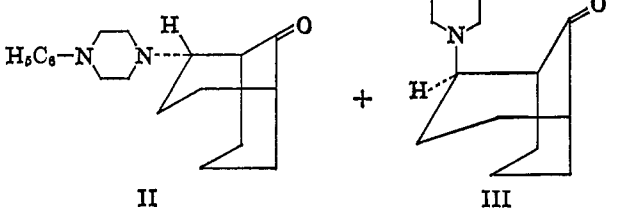
Compd.	R	R_1	R_2	n	Method[a]	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
II[b] and III	4-Phenyl-1-piperazyl	H	H	2	A	84	128–130	$C_{19}H_{26}N_2O$	76.51	8.72	9.40	76.26	8.45	9.61
V	4-Phenyl-1-piperazyl	CH_3	H	2	A	9	145–146	$C_{20}H_{28}N_2O$	76.92	8.97	8.97	77.23	9.29	8.92
VI	4-Phenyl-1-piperazyl	H	H	1	B	37	137–138	$C_{18}H_{24}N_2O$	76.06	8.52	9.86	75.88	8.78	10.07
VII	4-Phenyl-1-piperazyl	H	H	3	B	35	136–137	$C_{20}H_{28}N_2O$	76.87	9.05	8.97	76.61	9.10	9.00
VIII	4-Phenyl-1-piperazyl	H	C_6H_5	2	B	36	167–168	$C_{25}H_{30}N_2O$	80.07	8.06	7.47	80.27	8.24	7.58

[a] Method A is the rearrangement of aminohexahydrobenzopyrans; method B is the direct isolation of product from the reaction of enamine and α,β-unsaturated aldehyde. [b] Compound II is the preponderant isomer.

of the bicyclic amino ketones was assigned on the basis of the following evidence: sodium borohydride reduction of II gave one of the two possible amino alcohols in 75% yield; its infrared spectrum exhibited bands due to free and bonded OH at 3620 and 3440 cm.$^{-1}$, respectively. Reduction of III gave an amino alcohol (76% yield) whose infrared spectrum showed no free OH but rather a broad intense band centered at 3175 cm.$^{-1}$. This spectral result indicates strong intramolecular hydrogen bonding. Assuming the double-chair conformation for the bicyclo[3.3.1]nonane system,[5,6] such hydrogen bonding would be possible only with an axially oriented amino group.[7]

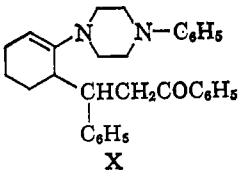


I



II III

An excellent method for the synthesis of $\Delta^{1,9}$-2-octalones involving the reaction of cyclohexanone enamines with alkyl vinyl ketones was developed by Stork and co-workers.[8] However, with aryl vinyl ketones the reaction would have to stop at some intermediate stage. Addition of chalcone to a solution of 1-(1-cyclohexen-1-yl)-4-phenylpiperazine in dry benzene resulted in the formation of the aminohexahydrobenzopyran (IX) in 44% yield. Again the characteristic enol ether band was present at 1660 cm.$^{-1}$. Isomerization to the enamino ketone X was accomplished



X

by merely recrystallizing a sample of IX from alcohol. The infrared spectrum of X showed bands at 1685 (aromatic C=O) and 1645 cm.$^{-1}$ (enamine C=C). The position of the double bond in compound X was assigned on the basis of the n.m.r. spectrum which exhibited a signal due to one vinylic hydrogen at τ = 5.09 p.p.m.[8,9] Treatment of the enamino ketone X with dilute acid at room temperature afforded 3-(2-oxocyclohexyl)-3-phenylpropiophenone.[10] Catalytic hydrogenation of X produced 3-phenyl-3-[2-(4-phenyl-

(5) 19th International Congress of Pure and Applied Chemistry, *Chem. Ind.* (London), 1345 (1963).

(6) W. Schneider and H. Gotz, *Ann.*, **653**, 85 (1962).

(7) For a discussion of the infrared spectra of intra- and intermolecularly N · · · HO bonded systems, see A. R. H. Cole in "Technique of Organic Chemistry," Vol. XI (Part I), A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 3.

(8) G. Stork, A. Brizzolara, H. Landesman, J. Muszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(9) M. E. Kuehne, *ibid.*, **81**, 5400 (1959).

(10) C. F. H. Allen and H. R. Sallans, *Can. J. Res.*, **9**, 574 (1933).

1-piperazyl)cyclohexyl]propiophenone (XI). We have not been able to convert the products derived from aryl vinyl ketones and cyclohexanone enamines into the expected bicyclic amino ketones.

Experimental[11]

Preparation of Enamines.—A solution of 1 mole of secondary amine, 1 mole of cycloalkanone, and 1 g. of *p*-toluenesulfonic acid in 300 ml. of toluene was heated under reflux for 1 day. The water liberated was collected in a Dean–Stark trap. The solvent was distilled and the residue was either distilled *in vacuo* or recrystallized from 2-propanol. The enamines tend to decompose on standing and should be purified just prior to use.

1-(1-Cyclohexen-1-yl)-4-phenylpiperazine was prepared in 84% yield, b.p. 125–140° (0.2 mm.), m.p. 112–114° from 2-propanol.

Anal. Calcd. for $C_{16}H_{22}N_2$: N, 5.72 (basic). Found: N, 5.92.[12]

1-(1-Cyclopenten-1-yl)-4-phenylpiperazine was prepared in 61% yield, m.p. 101° from 2-propanol.

Anal. Calcd. for $C_{15}H_{20}N_2$: N, 12.27 (total). Found: N, 12.40.

1-(1-Cyclohepten-1-yl)-4-phenylpiperazine was prepared in 27% yield, b.p. 140–180° (0.2 mm.), m.p. 59–61° from 2-propanol.

Anal. Calcd. for $C_{17}H_{24}N_2$: N, 10.92 (total). Found: N, 11.09.

4a,5,6,7,8,8a-Hexahydro-8a-(4-phenyl-1-piperazyl)-4H-1-benzopyran (I).—To a stirred solution of 14.1 g. (0.0583 mole) of 1-(1-cyclohexen-1-yl)-4-phenylpiperazine in 50 ml. of dry benzene was added a solution of 4.5 g. (0.080 mole) of acrolein in 25 ml. of dry benzene over a 30-min. period (5–10°). The solution was stirred at this temperature 1 hr., allowed to stand at room temperature 5 hr., then stored overnight in the refrigerator. The white crystals which had formed were collected and washed with a small amount of benzene–ether to give 4.6 g. of I: m.p. 117–118°; $\nu_{max}^{CHCl_3}$ 1660 (—O—CH=CH—), 1150, and 1070 cm.$^{-1}$ (ether). The n.m.r. spectrum ($CDCl_3$) showed resonance peaks due to the 2- and 3-protons at τ = 3.87 (doublet) and 5.41 p.p.m. (multiplet), respectively.

The benzene–ether filtrate from above was concentrated *in vacuo* to give a white solid. Recrystallization from benzene–hexane produced 7.6 g. of crystals, m.p. 113–114°, undepressed when mixed with an analytical sample of the aminopyran. The total yield was 12.2 g. (71%).

2-(4-Phenyl-1-piperazyl)bicyclo[3.3.1]nonan-9-one (Mixture of Isomers II and III).—To a solution of 9.03 g. of I in 100 ml. of freshly distilled dimethylformamide was added 3.1 g. of triethylamine. The solution was heated in a nitrogen atmosphere for 12 hr. at 70–75°. The solvents were distilled *in vacuo* and the residue was stirred with hexane. The crude solid weighed 7.61 g., m.p. 100–105°, $\nu_{max}^{CHCl_3}$ 1710 cm.$^{-1}$ (ketone C=O). Recrystallization from hexane and a few drops of benzene followed by recrystallization from a small quantity of methanol produced an analytical sample, m.p. 128–130°.

Separation of Isomers II and III.—A 21.2-g. sample of crude bicyclic amino ketone (obtained on concentration of the solvent used in the isomerization reaction) was dissolved in benzene and chromatographed on 350 g. of Brockmann activity I neutral alumina. Elution with benzene–ether (1:1) gave 20.0 g. of crystalline material (total from thirteen 125-ml. fractions). Thin layer chromatography on Merck aluminum oxide G[13] using benzene–ether (1:1) as developer showed fractions 2 and 3 (14.5 g.) to consist mainly of compound II. Recrystallization from methanol produced an analytical sample of the equatorial isomer (II), m.p. 129–130°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.51; H, 8.72; N, 9.40. Found: C, 76.39; H, 8.74; N, 9.50.

Fractions 4–6 (4.0 g.) were mixtures of II and III while fractions 7–13 (1.51 g.) consisted of compound III. An analytical sample of the axial isomer (III) was prepared by recrystallization from methanol, m.p. 100–101°; a mixture melting point with the equatorial isomer (II) was depressed, 85–90°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.51; H, 8.72; N, 9.40. Found: C, 76.62; H, 8.58; N, 9.46.

Sodium Borohydride Reduction of II.—A 1.00-g. sample of the amino ketone II was dissolved in 50 ml. of ethanol and treated with 1.2 g. of sodium borohydride. The mixture was heated under reflux 1 hr. after which excess hydrochloric acid was added. The solvent was distilled *in vacuo* and the aqueous mixture was made alkaline. A chloroform extract of the free base was concentrated *in vacuo* and the residual material was stirred with pentane to produce 0.75 g. of amino alcohol, m.p. 128–130°, $\nu_{max}^{CHCl_3}$ 3620 (free OH) and 3440 cm.$^{-1}$ (bonded OH).

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 76.00; H, 9.40; N, 9.33. Found: C, 75.80; H, 9.20; N, 9.25.

Sodium Borohydride Reduction of III.—A 0.17-g. sample of the amino ketone III in 10 ml. of ethanol was treated with 0.5 g. of sodium borohydride. The amino alcohol was isolated as described in the preceding experiment, yield 0.13 g., m.p. 145–147°. The infrared spectrum (10% in $CHCl_3$) showed no free OH absorption, but strong absorption centered at 3175 cm.$^{-1}$ was present (bonded OH). The intramolecular nature of this hydrogen bonding was shown by the fact that no free OH absorption appeared when the spectral solution was diluted.[7]

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 76.00; H, 9.40; N, 9.33. Found: C, 75.33; H, 9.24; N, 9.17.

3-Phenyl-3-[2-(4-phenyl-1-piperazyl)-2-cyclohexenyl]propiophenone (X).—A sample of the aminopyran IX (m.p. 129–130°, $\nu_{max}^{CHCl_3}$ 1660 cm.$^{-1}$) was recrystallized from methanol to give compound X in 60% yield, m.p. 135–136°, $\nu_{max}^{CHCl_3}$ 1685 (aromatic C=O) and 1645 (w, enamine C=C) cm.$^{-1}$. The n.m.r. spectrum ($CDCl_3$) showed a triplet centered at τ = 5.09 (vinyl proton) p.p.m. The analytical sample was prepared by a further recrystallization from ethanol, m.p. 134–135°; a mixture melting point with IX was depressed, 124–126°.

Anal. Calcd. for $C_{31}H_{34}N_2O$: C, 82.66; H, 7.56; N, 6.22. Found: C, 82.36; H, 7.63; N, 6.25.

3-Phenyl-3-[2-(4-phenyl-1-piperazyl)cyclohexyl]propiophenone (XI).—A 10.0-g. sample of compound X was dissolved in 250 ml. of ethyl acetate and hydrogenated in the presence of 3 g. of 10% palladium on charcoal (room temperature, 50 p.s.i.). After 12 hr., the catalyst and precipitated product were collected. The mixture was heated in ethyl acetate and the catalyst was filtered. Leaf-like crystals collected in the filtrate, yield 4.7 g., m.p. 176–177°. The filtrate, on concentration, yielded an additional 2.3 g. of product; the total yield of XI was 7.0 g. The infrared spectrum ($CHCl_3$) showed a strong band at 1685 cm.$^{-1}$ (aromatic C=O). The band at 1645 cm.$^{-1}$ (due to C=C) in the spectrum of X was absent. An analytical sample of XI was prepared by recrystallization from ethyl acetate, m.p. 176–177°.

Anal. Calcd. for $C_{31}H_{36}N_2O$: C, 82.30; H, 7.96; N, 6.19. Found: C, 82.10; H, 7.89; N, 6.17.

Acknowledgment.—The authors wish to thank Dr. Charles D. Hurd of Northwestern University for helpful discussions during the course of this work and Dr. Dale A. Stauffer and associates for the analytical services.

(11) Melting points were taken with a Büchi capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. The n.m.r. spectra were determined at 60 Mc. with a Varian Model A-60 spectrometer.

(12) Basic nitrogen values were determined by nonaqueous titration.

(13) Distributed by Brinkmann Instruments, Inc., Great Neck, Long Island, N. Y.

Lupenone and 18α-Oleanan-19α-ol-3-one from *Samadera indica*

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Interest in the constituents of *Samadera indica* Gärtn. (*Simarubaceae*), a tree found in Ceylon, India, and Java, originally centered on the bitter principle samaderin, first isolated in crystalline form by van