amount of anhydrous ether. The hydrochloride salt was precipitated as a gelatinous solid. This was dissolved in 100 ml of acetone and concentrated *in vacuo* until the solution became turbid. After cooling, 30 mg (48%), of white solid was collected, mp 212–214°. Two recrystallizations from ethanol–ether yielded analytical material, mp 215–216°. A mixture melting point with the *trans* amino alcohol hydrochloride XIVd was depressed to 175–185°; *cf* also Table XI.

N → O Acyl Migration of *cis*-2-Benzoylamino-2-phenylcyclohexanol, XVIIIc.—To 50 mg of XVIIIc prepared by the N-benzoylation of XVIIIa was added 2 ml of isopropyl alcohol saturated with dry hydrogen chloride. The resultant mixture was allowed to stand at room temperature for 114 hr, and then evaporated to dryness *in vacuo*. An infrared spectrum of the remaining hygroscopic solid showed essentially complete acyl migration as indicated by the strong absorption band at 5.85 μ (ester) and none at 6.02 μ (amide).

Attempted N → O Migration of XIVh.—A solution of 0.1 g of XIVh in isopropyl alcohol saturated with dry hydrogen chloride gas was allowed to stand for 114 hr at room temperature and worked up as above. An infrared spectrum of the reaction mixture at this point showed only the initial amide absorption band at 6.02 μ with no carbonyl absorption in the 5.85-μ region (ester C=O). Further work-up yielded 97% of the starting amide XIVh.

***trans*-2-(N-Methylacetamido)-2-phenylcyclohexanol, XVd.**—Amino alcohol XIVb[1a] (5.22 g, 0.025 mole) was dissolved in 150 ml of freshly distilled triethyl amine and the solution cooled to 0°. One equivalent (2 ml) of acetyl chloride was dissolved in 100 ml of benzene and added very slowly to the amide solution. Throughout the 3-hr addition the temperature was kept at 0° and the reaction mixture stirred magnetically. The mixture was then allowed to come slowly to room temperature and then stirred an additional 2 hr. Ethanol (2 ml) was added; all solvents were removed *in vacuo*. The resulting sludge was washed three times with 100-ml portions of benzene, each washing being filtered. The benzene was removed *in vacuo* and the resulting oil crystallized from chloroform–petroleum ether to give 2.64 g (44%) of XVd, mp 120–5°. Recrystallization afforded white crystals: mp 124–6°; infrared ($CHCl_3$) 2.90 and 6.05 μ. *Cf.* also Table XI.

***cis*-2-Methylamino-2-phenylcyclohexanol, XVIIIb.**—In 50 ml of freshly distilled, colorless thionyl chloride was dissolved XVb (1.6 g, 0.0065 mole). The solution was heated with magnetic stirring at 50 ± 5° for 8 hr and then allowed to stand overnight. The solution was poured on ice and stirred manually until the evolution of hydrogen chloride ceased. The pH of the solution was raised to 12 with potassium hydroxide and all organic material extracted with chloroform. The chloroform was removed *in vacuo* and the residue heated in a steam bath with 50 ml of 6 *N* hydrochloric acid overnight. Neutrals were removed by chloroform extraction; the pH of the solution was raised to 12. The bases were extracted with chloroform; the layer was dried over anhydrous potassium carbonate. The chloroform was then removed *in vacuo* and the residue dissolved in ether. Addition of 2-propanol–hydrogen chloride solution gave no crystals and so all solvents were removed *in vacuo*. Crystals were obtained from a solution of acetone–ethyl ether–petroleum ether (1.085 g, 68%, mp 199–204°). Recrystallization gave XVIIIb (HCl), mp 203–205°.

The free base was obtained in the usual fashion. All attempts to crystallize the compound failed and so the compound was distilled at approximately 100° (0.05 mm) to give a clear gum; *cf.* Table XI.

Conversion of *trans* Alcohol XIVa to *trans* Alcohol XIVd.—Acylation of 75 mg of XIVa was effected with propionic anhydride by standard procedure. The product, an oil, had infrared absorption at 6.02 μ and was not characterized further. The oil was dissolved in 30 ml of ether and refluxed with 40 mg of lithium aluminum hydride for 12 hr. Work-up afforded a basic fraction from which was isolated 60 mg (76%) of XIVd hydrochloride, mp 220–222°. Mixture melting point with a sample prepared by reduction of IIId was not depressed.

Acknowledgment.—A portion of this work was supported by the Parke, Davis & Co. until October 1, 1963. After that date a portion of this work was supported by the National Science Foundation Grant GP-205. This financial assistance is gratefully acknowledged.

Amino Ketone Rearrangements. VII.[1] Synthesis of 2-Methylamino-2-Substituted Phenylcyclohexanones

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Received March 14, 1966

The synthesis of a variety of 2-methylamino-2-substituted phenylcyclohexanones by thermal rearrangement of α-amino ketones, α-hydroxy imines, and imine salts is described. Some chemistry related to those compounds bearing *o*-phenyl substituents is also described.

The preceeding paper describes the synthesis of aminocyclohexanones of type III, by thermal rearrangement of isomers of type I and IV, wherein the nitrogen substituent was varied. This paper reports results of a similar type wherein phenyl substituents were varied. In general, the synthetic techniques described in paper VI were successfully extended to the present series of compounds, but important chemical differences related to the obvious structural differences were noted, and these are emphasized in the discussion following. (See Scheme I.)

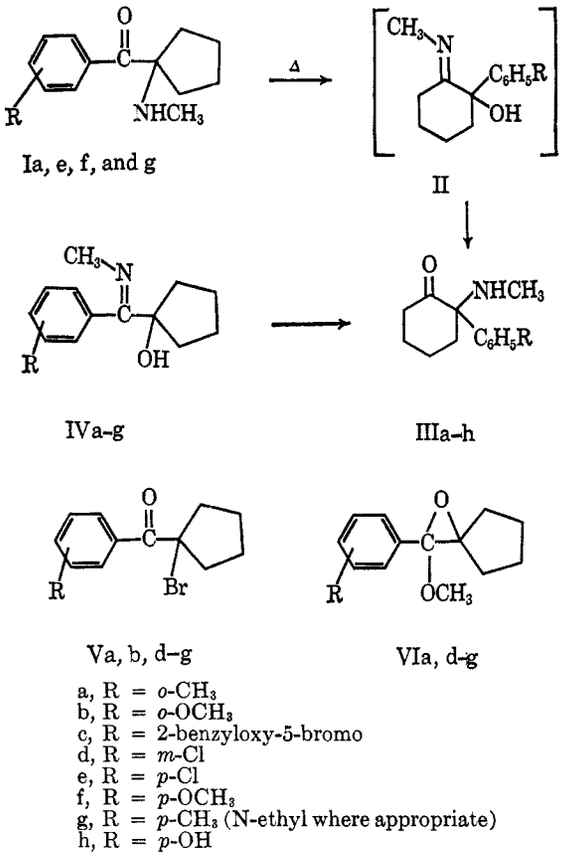
Syntheses.—The conjugated amino ketones I were prepared as previously described.[1] Hydroxy imines IV with the exception of IVa were prepared by the method of Stevens and co-workers.[1,3] The *ortho*-phenyl substituents on bromo ketones Va, b, and c afforded varying results on reaction with liquid methylamine. These reactions were, with the exception of Va, synthetically useful for preparation of the desired hydroxy imines IVb and c since these could be isolated by crystallization. Thus, IVb and c were prepared in 66 and 63% yield, respectively. On the other hand, synthesis of hydroxy imine IVa by this route failed, with amino ketone Ia being the only product isolated (67%). Further, the reaction of bromo ketone Va in methylamine at −6° had a half-life of about 2 min and produced no neutral products. By

(1) Paper VI: see accompanying publication, *J. Org. Chem.*, **31**, 2593 (1966).

(2) (a) NATO Fellow, 1961–1962. (b) Taken in part from the doctoral dissertations of H. T. Hanson and R. M. Weier.

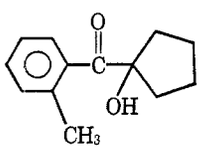
(3) C. L. Stevens, P. Blumbergs, and M. E. Munk, *J. Org. Chem.*, **28**, 331 (1963).

SCHEME I



a, R = *o*-CH_3
b, R = *o*-OCH_3
c, R = 2-benzyloxy-5-bromo
d, R = *m*-Cl
e, R = *p*-Cl
f, R = *p*-OCH_3
g, R = *p*-CH_3 (N-ethyl where appropriate)
h, R = *p*-OH

these two characteristics, the reaction of Va was very similar in nature to those reactions which had produced hydroxy imine. However, the yield of imine IVa in this reaction was judged (by infrared) to be very low. Satisfactory alternate synthesis for IVa was provided by the reaction of hydroxy ketone VII with methyl-



VII

amine. Compound VII in turn was prepared from epoxy ether VIa by a known procedure.[4] An interesting note here is that that bromo ketone which displayed such a high proportion of displacement at the α-position with methylamine (Va) still afforded a 91% yield of epoxy ether VIa on reaction with sodium methoxide in methanol at room temperature. An explanation for this duplicity is not yet available. It appears, however, that the formation of amino ketone Ia in preference to hydroxy imine IVa cannot be ascribed solely to steric hindrance of attack by amine at the carbonyl group of bromo ketone Va. For if this were the case one should expect at least qualitatively similar results from the reaction with sodium methoxide.

Rearrangements.—Qualitative rearrangement studies were done on three α-amino ketones, I. Interestingly, the only *ortho*-substituted amino ketone tested, Ia, failed to undergo rearrangement to IIIa. The *o*-tolyl series I–IVa was studied in some detail and is described separately below. In the remaining cases where rearrangement occurred the results, which are listed in Table I (runs 1 and 2) were similar to the analogous cases previously described.[1] Again, where comparisons were made, the hydroxy imines IV rearranged to cyclohexanones III in significantly higher yield than did the isomeric amino ketones (compare runs 9 and 10 with 1 and 2, Table I). And, in the two cases listed hydroxy imine salts afforded better rearrangements than did the corresponding free bases (runs 3 and 5). This fact has also been previously noted.[1]

TABLE I

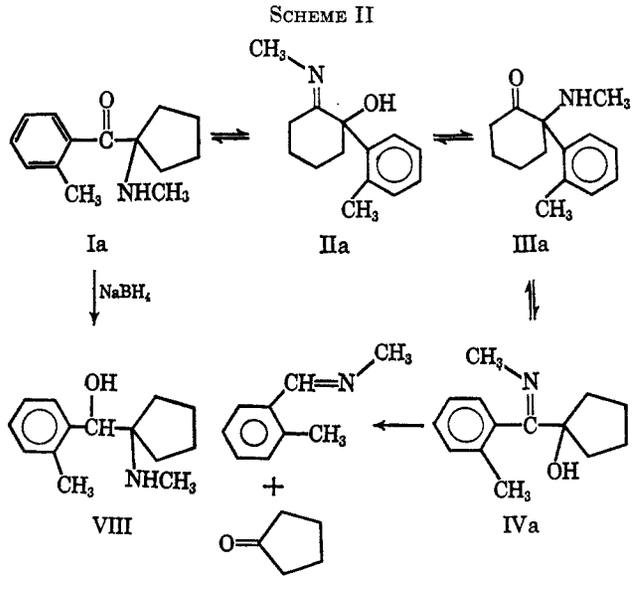
REARRANGEMENT REACTIONS, CONDITIONS AND YIELDS

Run	Compd (salt)	Temp °C (hr)	Solvent	Product	Yield, %
1	If[a]	210 (12)	Methylamine	IIIf	24
2	Ig[a]	200 (14)	Neat	IIIg	26
3	IV[b]	190 (3.3)	Decalin	IIIb	45[b]
4	IV[b] (HCl)	165 (1.5)	*o*-dichlorobenzene	IIIb	61[b]
5	IV[c]	190 (12)	Decalin	IIIc	60[b]
6	IV[c] (HBr)	160 (0.75)	*o*-dichlorobenzene	IIIc	81[c]
7	IVd	195 (2)	Hendecane	IIId	45[b]
8	IVe	195 (2)	Hendecane	IIIe	64
9	IVf	190 (2.7)	Decalin	IVf	62[b]
10	IVg	195 (2.5)	Hendecane	IIIg	55

[a] Experimental details in Experimental Section. [b] Isolated as hydrochloride salt. [c] Isolated as hydrobromide salt.

The *o*-Tolyl Series, Ia–IVa.—As was mentioned above, thermolysis of amino ketone Ia failed to produce any aminocyclohexanone IIIa. Thus, heating Ia at 195 and 235° (in hendecane and tridecane respectively) resulted only in decomposition products. The reaction progress was monitered at both temperatures by infrared and at no time did the characteristic cyclohexanone carbonyl absorption appear. After 40 hr at 195° a 17% recovery of Ia was obtained. This failure to rearrange prompted verification that the amino group was indeed located in a position α (as opposed to β) to the conjugated carbonyl group (5.9 μ) of Ia. An nmr spectrum of the hydrochloride salt of amino alcohol VIII (in D_2O) revealed the benzylic proton at τ 4.89 as a sharp singlet indicating no adjacent CH function. (See Scheme II.)

SCHEME II



(4) C. L. Stevens, M. L. Weiner, and R. C. Freeman, *J. Am. Chem. Soc.*, **75**, 3977 (1953).

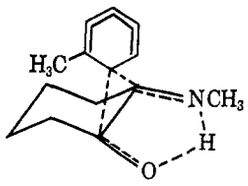
When rearrangement of IVa under the usual conditions gave low yields of the desired amino ketone IIIa and rather large amounts of decomposition, the use of organic acids as solvents was investigated using conditions similar to those described by Elphimoff-Felkin.[5] While anhydrous formic acid was found even less satisfactory than hydrocarbon solvents, anhydrous acetic acid was found to give slightly better yields in less time. However, in every case of rearrangement the reaction mixture rapidly turned black and IIIa was the only identifiable product which retained the entire carbon skeleton. Table II summarizes the rearrangements.

TABLE II

THE REARRANGEMENT OF 1-(α-METHYLIMINO-*o*-METHYLBENZYL)CYCLOPENTANOL, IVA

Run	Solvent	Temp, °C	Time, hr	% yield of IIIa	Remarks
1	*n*-Decane	166	9	42	Trace of cyclopentanone DNP could be isolated from exhausted helium gases
2	*n*-Tridecane	235	1	21	
3	Decalin	190	3.5	29	44% of o-tolualdehyde DNP isolated after hydrolysis
4	Acetic acid	119	3	44	
5	Formic acid	100	3	29	

When IIIa was prepared its thermal stability at 190° (decalin) was tested. The products of decomposition were cyclopentanone which was trapped as its 2,4-dinitrophenylhydrazone from the exhausted helium gases[6] and the N-methylimine of *o*-tolualdehyde. The presence of the imine decomposition product was evidenced by the development of a band in the infrared at 6.1μ and the fact that while no odor of benzaldehyde could be detected in the reaction mixture before an acidic hydrolysis, a strong odor was noticed after hydrolysis and *o*-tolualdehyde could be isolated in good yield (71%) at this point. The discovery of cyclopentanone and *o*-tolualdehyde N-methylimine as direct decomposition products indicated that the decomposition of the six-membered ketone IIIa had proceeded through ring contraction to imine IVa which, in turn, had fragmented.[7] A certain extent of fragmentation was also seen when the hydroxy imine IVa was the starting material (see run 3, Table II). It has been reported[8] that for the phenyl case (no substituent on phenyl) the comparable I ⇌ II and IV → III rearrangements proceed at similar rates. This data, together with the fact that IVa and IIIa readily interconvert, leads one to the conclusion that the failure of amino ketone Ia to rearrange to IIIa lies not in the Ia–IIa ring expansion, but rather in the IIa → IIIa aryl migration. Inspection of molecular models indicates that the *o*-tolyl group of IIa must migrate with its C-methyl group either protruding into the six-membered carbocyclic ring or else into the five-membered heterocyclic quasi-ring described by the nitrogen and oxygen functions; *cf* structure IX.



IX

Since the compounds of the *p*-methyl series, Ig–IVg, rearrange normally, the failure of the II–III interconversion can be ascribed to the steric requirements of the migrating *o*-tolyl group.[9] It is also of interest to note that for the phenyl case previously reported[8] the ring expansion of IV (no phenyl substituent) to III was irreversible.

Hydroxy Substituents.—Synthesis of phenolic derivatives was accomplished through the rearrangement of suitable precursors wherein the phenol function was covered by ether formation. Thus, the *p*-methoxy derivative IIIf was a suitable precursor for IIIh. Treatment of IIIf with refluxing acetic acid–hydrogen bromide cleaved the ether function and afforded IIIh in 81% yield. Compound IIIh had salt-like characteristics being a high melting (mp 157°), crystalline solid, soluble only in polar organic solvents in its free base (presumably zwitterionic) form.

The above-described hydrolysis conditions failed to cleave the ether group of the *o*-methoxy isomer IIIb. In fact, the group was not cleaved under a variety of vigorous, acidic conditions including refluxing hydriodic acid. In these cases starting material was usually recovered in yields greater than 50% with decomposition accounting for the balance.[10] In this light a more easily removed protecting group was sought. The benzyl group was tried and found to be satisfactory. The desired *o*-benzyloxyphenyl cyclopentyl ketone Xa was readily prepared *via* the Grignard reaction between *o*-benzyloxyphenylmagnesium bromide and cyclopentyl nitrile. While low temperature acidic bromination conditions were satisfactory for preparing bromo ketone Vb, the hydrogen bromide liberated under such conditions cleaved the benzyl group of Xa. Ketone bromination under buffered conditions (acetic acid-sodium acetate) was slower enabling nuclear bromination to compete, and, under these conditions, compound Xa consumed 2 mole equiv of bromine and yielded Xb. The subsequent reaction leading to IVc proceeded normally and the rearrangement conditions and yields of IIIc are recorded in Table I. Sodium borohydride reduction of IVc afforded the corresponding amino alcohol. Sodium metaperiodate cleaved this amino alcohol and yielded the known 2-benzoyloxy-5-bromobenzaldehyde.[11] In this way the position of the nuclear bromine atom of Xb was established. Cleavage of the benzyl protecting group of IIIc was facile being effected in refluxing hydrobromic acid and affording XIa in yields up to 92%. An infrared spectrum of XIa had no carbonyl absorption thus indicating for it the hemiketal-type structure XI. Hydrogenolysis of the

(5) I. Elphimoff-Felkin, *Bull. Soc. Chim. France*, 653 (1962).

(6) All rearrangements in the o-tolyl series were run under slow helium sweep.

(7) This fragmentation reaction has been evidenced in certain other cases; *cf* ref 1.

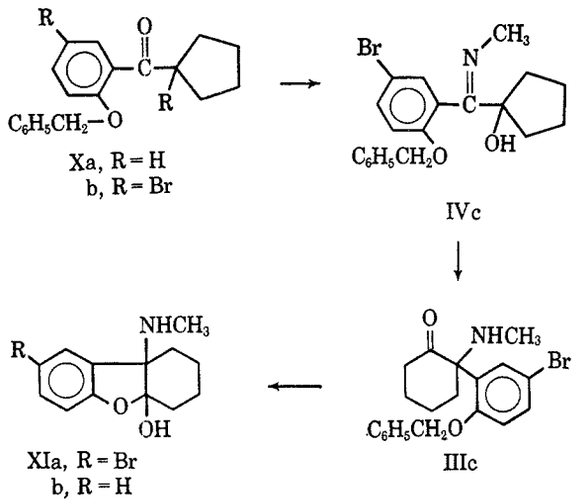
(8) C. L. Stevens, H. T. Hanson, and K. G. Taylor, *J. Am. Chem. Soc.*, **88**, 2769 (1966).

(9) The loss of migratory aptitude of the anisyl group by changing the substitution from *para* to *ortho* has been documented for the pinacol rearrangement: E. S. Gould, "Mechanism and Structure in Organic Chemistry, Rinehard and Winston, New York, N. Y., 1959, p 182.

(10) This resistance to cleavage is no doubt due to the closer proximity of the positively charged ammonium group in IIIb.

(11) L. C. Raiford and L. K. Tanzer, *J. Org. Chem.*, **6**, 730 (1941).

SCHEME III



nuclear bromine atom of XIa could be done using 20% palladium-on-carbon catalyst giving XIb in 80% yield.[12] (See Scheme III.)

Experimental Section

All melting points are uncorrected and were obtained on a Thomas–Hoover capillary melting point apparatus. pK_a' values were obtained in 50% methanol–water on a titrimeter previously described.[13] Elemental analyses were done by Midwest Microlab, Inc. Hydrochloride salts, except where noted were prepared using saturated hydrogen chloride–2-propanol solution.

Cyclopentylphenyl Ketones.—The *p*-methoxyphenyl,[14] *m*-chlorophenyl,[15] and *p*-tolyl[15] ketones have been previously described. The remainder were prepared by standard techniques and are described in Table III.

TABLE III

CYCLOPENTYLPHENYL KETONES

Cyclopentylphenyl ketone	Prepn method[a]	Bp or mp, °C	—% carbon— Calcd	Found	—% hydrogen— Calcd	Found
o-Methyl[b]	A	73 (0.1 mm)	82.93	82.64	8.57	8.57
— DNP		71–72	61.94	61.88	5.47	5.64
o-Methoxy[c]	A	97 (0.08 mm)	76.44	76.64	7.89	7.61
— DNP		100–101	59.37	59.40	5.29	5.50
o-Benzyloxy[d]	A[e]	46–47	81.40	81.43	7.19	6.90
p-Chloro[f]	B	95 (0.1 mm)	69.07	69.05	6.28	6.37
— DNP		100–101	55.60	55.45	4.41	4.49

[a] Method A, aryl Grignard reagent with cyclopentylnitrile (I. Friedman and H. Schecter, *J. Org. Chem.*, **25**, 877 (1960) records the nitrile); method B, aryl nitrile with cyclopentylmagnesium bromide. [b] $n^{25}D$ 1.5730; d^{25}_4 1.048. [c] $n^{25}D$ 1.5428; d^{25}_4 1.130; λ_{max} (ethanol) 246, 300 mμ (ε 8070, 3650). [d] Flash distilled prior to crystallization, 170–175° (0.4 mm). [e] Grignard reagent prepared from *o*-benzyloxybromobenzene which has been previously described: R. C. Huston, A. Neeley, B. L. Fayerweather, H. M. D'Arcy, F. H. Maxfield, M. M. Ballard, and W. C. Lewis, *J. Am. Chem. Soc.*, **55**, 2146 (1933). [f] $n^{25}D$ 1.5570.

α-Bromo Ketones.—Bromo ketones Vd, f, and g have been previously described.[15] The remainder were prepared by bromination in chloroform or carbon tetrachloride and are described in Table IV. Procedural differences where pertinent are noted as footnotes in the table. Where the bromo ketones were difficult to purify, they were often used in the crude state.

TABLE IV

α-BROMO KETONES, V

Bromo ketone	Bp or mp, °C	—% carbon— Calcd	Found	% hydrogen Calcd	Found	% bromine —or oxygen— Calcd	Found
Va[a]	109–112 (0.008 mm.)	58.44	58.70	5.66	5.92	Br 29.91	29.69
Vb[b]	26–27	55.13	55.40	5.34	5.33	O 11.30	11.58
Vc[c]	59–61	52.07	52.27	4.15	4.14	Br 36.48	36.51
Ve	58–59	50.12	50.09	4.21	4.28	O 5.56	5.86

[a] Extreme instability toward light necessitated preparation, work-up, and distillation in the dark; usually used crude; $n^{25}D$ 1.5482 on distilled product. [b] Brominated at 0° and crystallized from hexane at −78°. [c] Prepared as described in Experimental Section.

1-(2-Benzyloxy-5-bromobenzoyl)-1-bromocyclopentane, Vc.—To a stirred solution of 5.0 g of Vc and 3.0 g of sodium acetate in 60 ml of glacial acetic acid was added 5.8 g of bromine in 10 ml of acetic acid. The dropwise addition was completed after 3 hr whereupon the reaction mixture was stirred an additional 5 hr. Then hydrogen chloride–2-propanol was added dropwise at 15–20-min intervals until all the bromine had reacted and the solution became abruptly acidic. At this point additional sodium acetate was added to buffer the reaction mixture. The acetic acid was distilled *in vacuo*, toluene being used to remove last traces of acid. The residue was triturated with ether and the triturate washed with two 10-ml portions of 10% sodium hydroxide solution. After drying, the ether was distilled *in vacuo* and the light brown, crystalline residue recrystallized from hexane to give 5.3 g (68%) of white crystals, mp 59–61°. The analysis is listed in Table IV.

Epoxy Ethers VI.—Epoxides VId, f, and g have been previously described.[15] 2-Methoxy-2-*o*-tolyl- (VIa) and 2-methoxy-2-*p*-chlorophenyl-1-oxaspiro[2.4]heptane (VIe) were prepared by the method of Stevens and Farkas[16] with the modification that the reactions were performed at ambient temperatures. Epoxy ether VIa was prepared in 91% yield and had bp 59–60° (0.1 mm); $n^{25}D$ 1.5120; d^{25}_4 1.099.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31; O, 14.66. Found: C, 76.83; H, 8.52; O, 14.44.

Treatment of VIa with benzoic acid in refluxing benzene afforded 1-*o*-methylbenzoyl-1-benzoyloxycyclopentane as a derivative, mp 91–2° after recrystallization from petroleum ether (bp 30–60°).

Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.89; H, 6.61.

Epoxy ether VIe was prepared in 76% yield and had bp 82° (0.2 mm); $n^{25}D$ 1.5623.

Anal. Calcd for $C_{13}H_{15}ClO_2$: C, 65.41; H, 6.33; O, 13.41. Found: C, 65.21; H, 6.45; O, 13.41.

As described for VIa above, VIe afforded 1-*p*-chlorobenzoyl-1-benzoyloxycyclopentane on benzoic acid treatment, mp 127–128° after recrystallization from *n*-heptane.

Anal. Calcd for $C_{19}H_{17}ClO_3$: C, 69.41; H, 5.21; Cl, 10.79. Found: C, 69.64; H, 5.35; Cl, 10.96.

1-Benzoyl-1-methylaminocyclopentanes, I.—Amino ketones I were prepared as described in paper VI.[1] These and their derivatives are described in Table V. Amino ketone Ia was usually prepared by the reaction of methylamine with bromo ketone Va and this is described separately below.

Reaction of 1-*o*-methylbenzoyl-1-bromocyclopentane, Va, with Methylamine. A. Preparative Run.—Distilled methyl amine was collected in a three-necked flask equipped with a potassium hydroxide drying tube and magnetic stirring. In one portion bromo ketone Va (403 mg, 0.00159 mole) was added and the solution stirred for 15 min. The reaction mixture was then cautiously treated with 25 ml distilled water and 25 ml of ethyl ether. Titration of the aqueous wash gave 98% of the theoretical amount of bromide ion. The ether layer was extracted with 4 *N* hydrochloric acid and this acid solution refluxed for 3 hr. The acid solution was then extracted with 25 ml of ether, raised to pH 12 with solid potassium hydroxide, and extracted with two 25-ml portions of ether. This ether extract was dried and the hydrochloride salt precipitated. This process yielded 255 mg (67%) of amino ketone Ia hydrochloride, mp 161–162°.

B. Kinetic Runs.—Weighed samples of bromo ketone were treated at the prescribed temperature with 10 ml of methyl-

(12) Several examples of hydrogenolysis of an aryl halogen are cited in the literature: H. Kammerer, L. Horner, and H. Beck, *Ber.*, **91**, 1376 (1958); F. W. Neumann, N. B. Sommer, C. E. Kaslow, and R. L. Shriner, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 519.

(13) A. M. Wilson and M. E. Munk, *Anal. Chem.*, **34**, 443 (1962).

(14) D. Y. Curtin and S. Schmukler, *J. Am. Chem. Soc.*, **77**, 1105 (1955).

(15) C. L. Stevens, A. Thuillier, and F. A. Daniher, *J. Org. Chem.*, **30**, 2962 (1965).

(16) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 618 (1952).

TABLE V

PROPERTIES OF AMINO KETONES I AND THEIR DERIVATIVES

Amino ketone (salt)	Bp or mp, °C	—% carbon— Calcd	Found	% hydrogen Calcd	Found	% nitrogen Calcd	Found
Ia (HCl)[a,b]	161–162	66.26	66.06	7.94	7.73	5.52	5.74
Ie[b]	94 (0.07 mm)	65.75	65.71	6.80	6.73	5.90	6.06
Ie (HCl)[a,d]	153–154	56.94	57.07	6.25	6.47	5.11	5.03
If[e]	115 (0.06 mm)	72.07	71.83	8.21	8.23	6.01	6.26
If (HCl)[a,f]	167–168	62.31	62.47	7.47	7.60	5.19	5.32
Ig[g]	96–97 (0.07 mm)	77.88	77.92	9.15	9.03	6.06	6.06
Ig (HCl)[a,h]	196–197	67.27	67.05	8.28	8.29	5.23	5.24

[a] Recrystallized from ethanol–ether or ethanol–pentane. [b] pK_a' 7.33. [c] $n^{25}D$ 1.5574. Cl: calcd, 14.94; found, 14.76. [d] A higher melting crystalline form, mp 174–175°, was also obtained. [e] $n^{25}D$ 1.5565. [f] λ_{max} (ethanol) 224 and 286 mμ (ε 9500 and 16,400); pK_a' 7.55. [g] $n^{25}D$ 1.5357. [h] λ_{max} (ethanol) 254 mμ (ε 6000).

amine. At intervals individual reactions were quenched by partitioning between 50 ml of ether–water (1:1 v/v). The aqueous layer was titrated for bromide ion. Ether layers were evaporated and their infrared spectra obtained. Some titration results are listed in Table VI.

TABLE VI

Temp, °C	Time, min	% reaction	~k, sec^{-1}
−6	2	57	0.18
	3	74	0.20
	5	87	0.18
	15	99	0.13
	30	100	av. 0.17
−78	30	19	0.003
	300	96	0.004

Infrared spectra of the 5- and 15-min (−6°) reaction showed only a shoulder in the 6.05-μ region (C=N region). An infrared spectrum of a complete reaction at −40° showed an estimated 30% of imine IVa. Isolation at this point was unsuccessful.

Hydroxy Imines, IV.—These hydroxy imines were prepared, with the exception of IVa, from bromo ketones V by the method illustrated in paper VI.[1] Their properties and derivatives are recorded in Table VII. All hydroxy imines exhibited strong infrared absorption at or near 3.1 and 6.05 μ.

1-Hydroxy-1-(*o*-methylbenzoyl)cyclopentane, VIII.—A suspension of 8.95 g (0.41 mole) of epoxy ether VIa in 50 ml of water was treated with 2 drops of concentrated hydrochloric acid and stirred overnight at room temperature. Extraction with ether followed by a bicarbonate wash and distillation of the ether afforded an oil. Subsequent fractionation (Vigreux column) yielded 5.98 g (71%) of colorless liquid: bp 83–84° (0.08 mm); $n^{25}D$ 1.5410; d^{25}_4 1.104; infrared (chloroform) 2.91 and 5.93 μ.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90; O, 15.66. Found: C, 76.63; H, 7.50; O, 15.80.

The semicarbazone had mp 169–70°.

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.36; H, 7.50; N, 16.23.

1-(α-Methylimino-*o*-methylbenzyl)cyclopentanol, IVa.—Hydroxy ketone VII (11.3 g, 0.055 mole) and redistilled methyl amine (120 ml) were heated in an autoclave for 12 hr at 95 ± 5°. The reaction residue was taken up in ether, evaporated *in vacuo*, taken up in hot hexane, dried over anhydrous potassium carbonate, treated with Norit, concentrated, and cooled to yield hydroxy imine IVa: 9.39 g (78%) as colorless crystals; mp 57.5–59°; infrared (chloroform) 3.08 and 6.08 μ.

Rearrangements.—Rearrangement conditions were similar to those described in paper VI.[1] Conditions and yields for all rearrangements are listed in Table I. The two amino ketone rearrangements (runs 1 and 2) required chromatography to isolate pure products.

In run 1 epoxy ether VIf (33.5 g) was heated in an autoclave with methylamine at 100° for 18 hr. The crude reaction product If, which represented a 100% material balance, was reheated in 75 ml of methylamine at 210° for 12 hr. The product after evaporating methylamine was subjected to a 3.5-hr hydrolysis in 50 ml of refluxing 4 *N* hydrochloric acid (to hydrolyze any imines formed during pyrolysis). The resulting basic oil was flash distilled and chromatographed on Florisil. Elution with petroleum ether (bp 30–60°) yielded 8.3 g of If as its hydrochloride salt. Elution with 10–30% acetone–petroleum ether yielded 8.5 g of IIIf as its hydrochloride, mp 210–15°. Recrystallization from ethanol–ether afforded 6.6 g (24% based on recovered If) of IIIf, mp 215–217°.

In run 2, Ig (8.1 g) was heated neat at 200° for 14 hr. Nonhydrolyzable basic material was chromatographed as the free base on Florisil. Elution with 50% hexane–petroleum ether afforded 2.1 g of Ig as its hydrochloride. Elution with 2:2:1 hexane–petroleum ether–acetone yielded 2.3 g (26%) of IIIg as its hydrochloride. Table VIII records the properties of aminocyclohexanones, III, and their derivatives. All amino ketones III had infrared maxima between 5.75 and 5.85 μ.

Reduction Products.—Using conditions described in reference 1, several amino ketones and hydroxy imines by way of characterization were reduced to their corresponding amino alcohols. These are recorded in Table IX. The products were generally isolated as salts and recrystallized from ethanol, ethanol–ether or methanol–ether.

***o*-Tolualdehyde from Thermolysis of IVa.**—Hydroxy imine IVa (3.38 g, 0.0155 mole) was dissolved in 40 ml of decalin and refluxed for a total of 3.5 hr. Eight 0.5-ml aliquots were withdrawn at intervals and their infrared spectra taken. At 3.5 hr the infrared spectrum indicated that the reaction had proceeded as far as one could expect and the reaction solution was extracted with 50 ml of 6 *N* hydrochloric acid and the extract was heated overnight on a steam bath. The neutral and the basic compounds were separated as usual. From the basic fraction, amino ketone IIIa was isolated as its hydrochloride salt [1.045 g, 29% (corrected for infrared samples), mp 264–266°]. The neutral extractions were obtained (730 mg, 44% as *o*-tolualdehyde) and converted to the 2,4-dinitrophenylhydrazone, mp 191–193°; mixture melting point with an authentic sample was undepressed.

Thermal Decomposition of 2-Methylamino-2-*o*-toluylcyclohexanone, IIIa.—An aqueous solution of IIIa hydrochloride (0.250 g, 0.00098 mole) was raised to pH 12 with potassium hydroxide and the free base extracted with chloroform which was then removed *in vacuo*. The residue was dissolved in 30 ml of redistilled decalin and refluxed (190°) under a helium sweep. Infrared spectra were taken periodically of the reaction solution. In 3 hr the intensity of the band at 5.75 μ was one-half as intense as it was at time zero and a strong band at 6.1 μ had developed. The band at 5.75 μ continued to be reduced and the 6.1 band increased as reaction proceeded. At 20 hr the bands achieved equal intensity. After 90 hr infrared indicated that the starting amino ketone had been almost completely destroyed. At no time was a band near 5.65–5.7 μ (cyclopentanones) observed. This infrared study consumed fifteen 1-ml samples. After 90 hr the remaining solution was extracted with 20 ml of 6 *N* hydrochloric acid and the extract heated on a steam bath overnight. After this hydrolysis, but not before, a strong odor of aromatic aldehyde was noted. The neutral fractions were obtained from the acid solution by ether extraction and the ether removed *in vacuo*. The residue was treated with 2,4-dinitrophenylhydrazine solution and 100 mg (71% corrected for infrared samples) of *o*-tolualdehyde 2,4-dinitrophenylhydrazone was obtained, mp 192–193°; mixture melting point with authentic sample was undepressed, after chromatography over alumina. No bands were seen on the column during chromatography except those of the isolated hydrazone and 2,4-dinitrophenylhydrazine itself.

The acid solution remaining after extraction of the neutral fractions was raised to pH 12 with potassium hydroxide and extracted with chloroform. Removal of the chloroform *in vacuo* gave a very small black smear from which no product could be obtained.

2-(*p*-Hydroxyphenyl)-2-methylaminocyclohexanone, IIIh.—A solution of 500 mg of amino ketone IIIf in 25 ml of dry acetic acid saturated with hydrogen bromide was heated at reflux for 12 hr. The solvent was distilled *in vacuo* affording a light brown solid. This was dissolved in methanol and poured onto a 1 × 10 cm Dowex 1-X2 (hydroxide form) column. Elution with methanol yielded 105 mg of starting IIIf. Elution with 50 ml of 1% methanolic hydrochloric acid yielded 200 mg of IIIh, mp 156–157°. Continued elution with 50 ml of the same solvent yielded 60 mg of IIIh, mp 153–156°. Total yield was 165 mg (81%

TABLE VII

1-(α-METHYLIMINOBENZYL)CYCLOPENTANOLS, IV, AND DERIVATIVES

Compd (salt)	Mp or bp, °C	Recrystn solvent	% carbon		% hydrogen		% nitrogen	
			Calcd	Found	Calcd	Found	Calcd	Found
IVa[a]	57–59	Hexane	77.38	77.57	8.81	8.82	6.45	6.65
IVb	77–78	Hexane	72.07	72.10	8.21	8.11	6.01	6.23
IVb (HCl)[b,c]	191–192	Ethanol–pentane	62.50	62.59	7.47	7.59	5.20	5.20
IVc	92–94	Hexane	61.86	61.92	5.71	5.87		
IVc (HBr)[c]	158–60	...						
IVd	97–98	Pentane	65.68	65.69	6.78	6.98	5.93	5.89
IVe	64–65	*n*-Heptane	65.68	65.43	6.78	6.97	5.93	5.66
IVf	38–39	Pentane	72.07	72.03	8.21	8.19		
IVg[d]	88–90 (0.01 mm.)	...	77.88	77.77	9.15	9.23	6.06	5.87

[a] pK_a' 6.70. [b] pK_a' 6.78. [c] Salts were prepared by methods similar to those described in ref 1. [d] $n^{25}D$ 1.5279.

TABLE VIII

2-METHYLAMINO-2-PHENYLCYCLOHEXANONES, III, AND THEIR SALTS

Compd (salt)	Mp or bp, °C	Recrystn solvent	% carbon		% hydrogen		% nitrogen	
			Calcd	Found	Calcd	Found	Calcd	Found
IIIa	56–58	Hexane	77.38	77.66	8.81	8.85	6.45	6.50
IIIa (HCl)[a]	265–266	Acetone–ether	66.26	65.99	7.94	7.84	5.52	5.62
IIIb	81–82	Hexane	72.07	72.16	8.21	8.21	6.00	5.80
IIIb (HCl)[b]	219–220	Ethanol–ether	62.31	62.43	7.47	7.70	5.19	5.49
IIIc (HBr)[c]	215–216	Ethanol–ether	51.18	51.44	4.95	5.11	2.98	2.95
IIId (HCl)	262–263	Ethanol–ether	56.94	57.07	6.25	6.36	5.11	5.38
IIIe[d]	116 (0.05 mm)	...	65.68	65.45	6.78	6.78	5.89	5.95
IIIe (HCl)	221–222	Ethanol–ether	56.94	56.80	6.25	6.38	5.11	5.11
IIIf (HCl)[e]	215–217	Ethanol–ether	62.31	62.27	7.47	7.48	5.19	5.07
IIIg[f]	107 (0.01 mm)	...	77.88	77.66	9.15	9.17	6.06	5.94
IIIg (HCl)[g]	232–234	Ethanol–ether	67.27	67.26	8.28	8.26	5.23	5.19
IIIh[h]	156–157	Methanol	71.21	71.16	7.81	7.85	6.39	6.39
IIIh[i]	213–214	Ethanol–ether	61.05	61.29	7.09	7.24	5.47	5.56

[a] pK_a' 7.50. [b] pK_a' 8.51. [c] Br: calcd, 34.06; found, 33.80. [d] $n^{25}D$ 1.5598; d^{25}_4 1.186. [e] λ_{max} (ethanol) 235, 275, and 282 mμ (ε 3440, 145, and 125). [f] $n^{25}D$ 1.5379. [g] λ_{max} (ethanol) 257, 262, and 268 mμ (ε 330, 359, and 272). [h] pK_a' 8.23 and 10.3. [i] λ_{max} (ethanol) 276 and 282 (sh) mμ (ε 150 and 125).

TABLE IX

SODIUM BOROHYDRIDE REDUCTION PRODUCTS OF I, III, AND IV

Compd reduced	Mp, °C, of product (salt)	pK_a'	% carbon		% hydrogen		% nitrogen	
			Calcd	Found	Calcd	Found	Calcd	Found
Ia	252–254 (HCl)	9.5	65.73	65.58	8.67	8.77	5.48	5.63
If[a]	121–122	...	71.43	71.59	9.00	9.07	5.96	5.97
Ig	245–246 (HCl)	...	66.77	66.64	8.97	8.87	5.19	4.97
IIIa[b]	238–240 (HCl)	7.65	65.73	65.68	8.67	8.46	5.48	5.49
IIIe[c]	224–225 (HCl)	...	56.53	56.80	6.93	7.02	...	...
IVa	160–161 (HCl)	9.0	65.73	65.52	8.67	8.67	5.48	5.33
IVb	196–197 (picrate)	...	51.74	51.73	5.21	5.33	12.07	11.86
IVe	176–177 (picrate)	...	48.79	49.00	4.31	4.58	11.94	12.02
IVf	168–169 (picrate)	...	51.74	51.66	5.21	5.34	12.07	11.88
IVg	155–157 (HCl)	...	66.77	66.78	8.97	9.02	5.19	5.17

[a] Recrystallized from acetone–petroleum ether. [b] Reduced in refluxing 2-propanol. [c] Cl: calcd, 25.68; found, 25.67.

based on recovered IIIf). Recrystallization of a portion from methanol gave analytical sample, mp 156–157°. Further details and the hydrochloride salt are in Table VIII.

9-Bromo-5-hydroxy-9b-methylamino-1,2,3,4,4a,9b-hexahydrodibenzofuran, XIa.—A solution of 2.5 g of IIIc hydrobromide in 130 ml of 24% hydrobromic acid was refluxed with stirring for 10 hr. Dissolution of the starting material was complete after 1 hr at the reflux temperature. The solvent was concentrated *in vacuo* to 3 ml whereupon the product XIa hydrobromide crystallized affording 1.9 g, mp 227–229°. Recrystallization from ethanol–ether afforded 1.7 g, mp 231–233°, of analytical material: infrared (mull) 2.85, 3.0, 6.13 and 6.23 μ.

Anal. Calcd for $C_{13}H_{17}Br_2NO_2$: C, 41.18; H, 4.53; N, 3.51. Found: C, 41.32; H, 4.64; N, 3.78.

5-Hydroxy-9b-methylamino-1,2,3,4,4a,9b-hexahydrodibenzofuran, XIb.—A solution of 1.7 g of XIa hydrobromide in ethanol was hydrogenated (1 atm) using 1.0 g of prereduced 20% palladium hydroxide on carbon as catalyst. After the theoretical amount of hydrogen uptake was observed, the uptake ceased. After filtration, evaporation of the solvent afforded a red gum which solidified on trituration with ether. Washing with ethyl acetate removed the red color and the product could be recrystallized from 2-butanol-ethyl acetate affording 1.15 g, mp 182–183°.

Anal. Calcd for $C_{13}H_{18}BrNO_2$: C, 52.01; H, 6.06; N, 4.66; Br, 26.61. Found: C, 51.99; H, 6.09; N, 4.85; Br, 26.64.

Structure Proof of IVc (Position of Nuclear Bromine).—A solution of 600 mg of hydroxy imine IVc in 15 ml of methanol was treated with 300 mg of sodium borohydride. The reaction was allowed to stand at room temperature overnight. Work-up was carried out by adding water to the reaction mixture and then acidifying with dilute hydrochloric acid. Evaporation of methanol *in vacuo* gave a water-insoluble solid which was saved. The aqueous acid layer was extracted with ether, then made basic with sodium hydroxide pellets and re-extracted with ether. This base fraction, however, yielded no material. The white, water-insoluble solid mentioned above was treated

at 100° with 10 ml of 6 *N* sodium hydroxide for 15 min. During the course of this heating, the solid disappeared and an oil separated. After cooling to room temperature, the aqueous layer was extracted three times with 20 ml of ether. After drying, evaporation of the ether yielded 250 mg of a white solid, mp 100–102.5°. A portion of this was recrystallized twice from hexane to give an analytical sample of the amino alcohol, mp 102–104°.

Anal. Calcd for $C_{20}H_{24}BrNO_2$: C, 61.53; H, 6.21; N, 3.58. Found: C, 61.48; H, 6.34; N, 3.71.

A solution of 100 mg of the above amino alcohol in 5 ml of methanol was treated with a solution of 110 mg of sodium metaperiodate in 7 ml of water. Enough methanol and water was added to make the solution homogeneous, bringing the final volume to 20 ml. The reaction was allowed to stand at room temperature under nitrogen ebullition for 5 hr. The inorganics were then removed by filtration and the methanol was evaporated *in vacuo*. The remaining aqueous layer was extracted twice with 15 ml of ether. After drying, evaporation of the ether *in vacuo* left a solid residue, mp 63–66°. Two recrystallizations from hexane yielded 15 mg, mp 70–72° (lit.[11] mp 73–74°).

Authentic 5-bromo-2-benzyloxybenzaldehyde was prepared from salicylaldehyde according to the procedure of Raiford and Tanzer.[11] A mixture melting point of the authentic sample with the material from the cleavage reaction was undepressed.

Acknowledgment.—A portion of this work was supported by Parke, Davis & Co. until October 1, 1963, and after that date a portion was supported by the National Science Foundation Grant GP-205. This financial assistance is gratefully acknowledged. The authors wish to thank Melvin Clark and John Stoddard for the synthesis of three compounds.

Quinazolines. III. Synthesis of 1,3-Diaminobenzo[*f*]quinazoline and Related Compounds[1-3]

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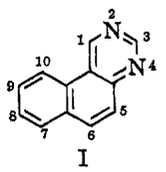
Received March 9, 1966

The title compound was prepared by condensation of 1-cyano-2-naphthylamine with cyanamide in the presence of pyridine hydrochloride, or by amination of 1,3-dichlorobenzo[*f*]quinazoline at elevated temperature and pressure. Similarly, reaction of formamide, urea, and thiourea with 1-cyano-2-naphthylamine afforded 1-amino-, 1-amino-3-hydroxy-, and 1-amino-3-mercaptobenzo[*f*]quinazoline, respectively. A novel reaction between guanidine and 2-hydroxy-1-naphthaldehyde resulted in the formation of 3-aminobenzo[*f*]quinazoline. A number of other previously unknown benzo[*f*]quinazolines, including the unsubstituted parent member of the series, were prepared by acid hydrolysis, thiation with phosphorus pentasulfide, and nickel-catalyzed dethiation reactions. The nuclear magnetic resonance spectrum of benzo[*f*]quinazoline is presented.

As a logical extension of earlier work[4] involving, in part, certain derivatives of benzo[*f*]quinazoline (I), a more thorough investigation of this ring system was undertaken. A review of the literature[5-15] revealed that only a few systematic studies dealing with benzo-



I

[*f*]quinazolines had been carried out previously. A major objective of the present study was to prepare 1,3-diaminobenzo[*f*]quinazoline (II) as a planar, tricyclic analog of the antifolic and antimalarial agent pyrimethamine (III).[16,17] The hypothesis that this type of structural modification might lead to enhanced biological activity is consistent with our earlier observation that the sterically related 4,6-diamino-1-aryl-1,2-dihydro-*s*-triazine molecule exhibits optimal anti-

(1) This investigation was supported in part by Research Grant C6516 and Research Career Development Award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

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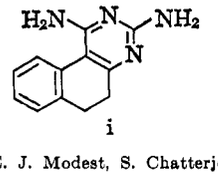

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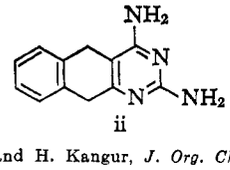

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