in ether. White crystals of V formed and were washed with a small portion of ether and dried at 70° (0.5 mm). The product consist of extremely hygroscopic, needlelike crystals. Melting point and analytical data are included in Table III.

Hydrolysis of γ,γ,γ-Trichloropropylene Oxide.—γ,γ,γ-Trichloropropylene oxide (2 g) was refluxed with 15 ml of water containing 5 drops of sulfuric acid for 4 hr. The mixture turned homogeneous and was extracted continuously with ether for 3 hr. 3,3,3-Trichloropropane-1,2-diol was obtained after the removal of ether in 20%. Recrystallization was performed with carbon tetrachloride, mp 84.6–85.0°.

Anal. Calcd for $C_3H_5Cl_3O_2$: C, 20.08. Found: C, 20.07.

Registry No.—IIIa, 13144-12-2; IIIb, 13144-13-3; IIIc, 13144-14-4; IIId, 13144-15-5; IVa, 13144-16-6; IVb, 13144-17-7; IVc, 13144-18-8; V, 13144-19-9; VI, 13144-20-2; 3,3,3-trichloropropane-1,2-diol, 815-02-1.

Synthesis of New Bicyclic Imines, Enamines, and Iminium Salts. I. The 1,4-Ethano-1,4-dihydro- and 1,2,3,4-Tetrahydroisoquinolines[1]

GORDON N. WALKER AND DAVID ALKALAY

Research Department, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey

Received December 30, 1966

Cyclization of γ-phenyl-δ-ketovaleric acids with sulfuric acid gives 4-acetyl-1-tetralones. 1-Monooximes or the dioximes of these are hydrogenated in the presence of palladium to give mixtures of diastereoisomeric 1-aminotetralins. The *cis*-amino ketones or amino oximes readily form dehydrobenzoisoquinuclideines (3,4-disubstituted 1,4-dihydro-1,4-ethanoisoquinolines). Quaternary iminium salts prepared from the bicyclic imines are converted by bases to bicyclic enamines (2,4-disubstituted 3-alkylidene-1,4-ethano-1,2,3,4-tetrahydroisoquinolines) and these are reconverted by acids to 2,3,4-trisubstituted 1,4-dihydro-1,4-ethanoisoquinolinium salts. A number of other reactions leading toward and defining the properties of 4-acetyl-4-phenyl-1-tetralone are described, including condensation with formaldehyde and secondary amine salts to give 2-(aminomethyl)-4-acetyl-1-tetralones, 2-nitrosation, selective reactions of the 1-tetralone group with hydrogen, glycol, and other reagents, and 2-bromination. 2-Bromo-4-acetyl-4-phenyl-1-tetralone undergoes a novel, base-catalyzed rearrangement, giving 2-acetyl-4-phenyl-1-naphthol.

Preceding papers[2,3] from our laboratory have dealt with syntheses of benzazepinones, benzomorphans, and oxindoles, in which the chemistry of functional groups appended to a quaternary carbon atom was investigated. Together with Schenker,[4] we have also been engaged in synthesis of quaternary carbon compounds having five- and six-membered bridged heterocyclic rings across the tetrahydronaphthalene ring system, incorporating amino groups attached to positions 1 and 2. The purpose of this paper is to describe the exploration of syntheses starting from tetralones which led to the finding of new bicyclic imines and enamines arising by the interaction of a 1-amino group with a ketone group attached at position 4.[5]

Unlike such well-known groups of nitrogen-bridged ring compounds as the tropanes and quinuclidines, the isoquinuclidines did not receive much attention until recently. As pointed out by Schneider,[6] this probably is because isoquinuclidines are of infrequent natural occurrence. Recently, there has been much interest in this type of bridged ring, however, owing to its presence in the *Tabernanthe iboga* alkaloids[7] and in dioscorine.[8] The classical preparation of isoquinuclidones through the 1,4-lactam bridging reaction[6,9] has been supplemented by the development of newer syntheses, notably dienophile addition to 1,2-dihydropyridines[7b,10] and more recently addition of 1,4-cyclohexadienes to methyleneurethans and other imine derivatives.[11] These later methods, however, do not lend themselves readily to synthesis of isoquinuclidines having bridgehead substituents, and the literature contains only an isolated example of synthesis of an isoquinuclidone bearing a bridgehead phenyl group.[12] Also, only recently has any effort been made to synthesize isoquinuclideines[13] and similar bridged imines.[14]

We approached the synthesis of bridged bases from functionally modified tetralones containing a qua-

(1) Presented in part at the Gordon Research Conference on Heterocyclic Compounds, New Hampton, N. H., July 5, 1966.

(2) (a) G. N. Walker, D. Alkalay, and R. T. Smith, *J. Org. Chem.*, **30**, 2973 (1965); (b) G. N. Walker and D. Alkalay, *ibid.*, **31**, 1905 (1966).

(3) G. N. Walker, R. T. Smith, and B. N. Weaver, *J. Med. Chem.*, **8**, 626 (1965).

(4) K. Schenker, Belgian Patent 665,189 (1965); Netherlands Patent Application, 6,507,339; *Chem. Abstr.*, **65**, 696 (1966); G. N. Walker and K. Schenker, U. S. Patent 3,291,806 (1966).

(5) Some of this work has already been revealed in Netherlands Patent Application 6,504,323 (1965); *Chem. Abstr.*, **64**, 8155 (1966). The 1,4-ethanohydroisoquinoline nomenclature is simpler and clearer in respect to position numbering than either of two alternatively possible names, benzoisoquinuclideine or 5,6-benzo-3-azabicyclo[2.2.2]octa-2,5-diene. For further clarity in this discussion, tetralone precursors and the ethanohydroisoquinolines ultimately obtained have also been numbered in a mutually consistent way.

(6) W. Schneider and R. Dillmann, *Ber.*, **96**, 2377 (1963).

(7) (a) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 126 (1958). (b) See the elegant ibogamine synthesis of G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *ibid.*, **87**, 2073 (1965); **88**, 3099 (1966), and additional references therein.

(8) W. A. M. Davies, J. G. Morris, and A. R. Pinder, *Chem. Ind.* (London), 1410 (1961).

(9) G. Wendt, *Ber.*, **75B**, 425 (1942); E. Ferber and H. Brückner, *ibid.*, **76B**, 1019 (1943); L. H. Werner and S. Ricca, *J. Am. Chem. Soc.*, **80**, 2733 (1958).

(10) O. Mumm and J. Diedrichsen, *Ann.*, **538**, 195 (1935); K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960, 1971 (1959); **45**, 1344 (1962); T. Agawa and S. I. Miller, *J. Am. Chem. Soc.*, **83**, 449 (1961); M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962). Cycloaddition of benzyne to a 1,2-dihydropyridine might serve as a synthesis of 5,6-benzo-3-azabicyclo[2.2.2]octa-5,7-diene-type compounds. The reaction of benzyne and pyrroles gives 7-azabenzonorbornadienes; see L. A. Carpino and D. E. Barr, *ibid.*, **31**, 764 (1966), and references therein. Reaction of N-methyl-2-pyridone and benzyne to give a benzodehydroisoquinuclideine was reported very recently by L. Bauer, C. L. Bell, and G. E. Wright, *J. Heterocyclic Chem.*, **3**, 393 (1966).

(11) M. P. Cava and C. K. Wilkins, *Chem. Ind.* (London), 1422 (1964); G. Kresze and R. Albrecht, *Ber.*, **97**, 490 (1964); M. P. Cava, C. K. Wilkins, D. R. Dalton, and K. Bessho, *J. Org. Chem.*, **30**, 3772 (1965).

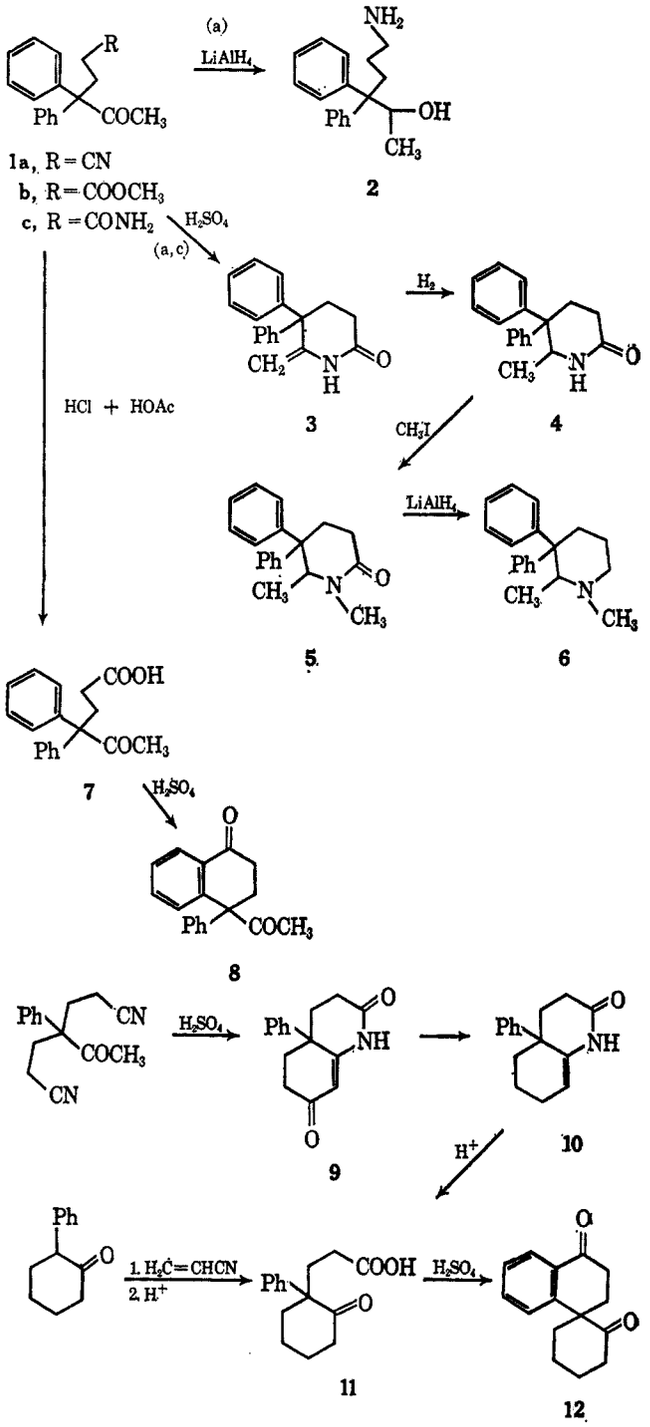
(12) C. F. Koelsch, *ibid.*, **25**, 164 (1960).

(13) See W. Schneider, R. Dillmann, E. Kämmerer, and K. Schilken, *Angew. Chem.*, **76**, 606 (1964), for mercuric acetate oxidation of isoquinuclidines, and W. Schneider, R. Dillmann, and H. J. Dechow, *Arch. Pharm.*, **299**, 397 (1966); *Chem. Abstr.*, **65**, 3832 (1966), for further reactions of simple isoquinuclideinium salts.

(14) P. M. Carabateas, A. R. Surrey, and L. S. Harris, *J. Med. Chem.*, **7**, 293 (1964).

ternary carbon atom in 1963 when some now available relevant literature on tetralones[15] had not yet appeared. In beginning this work we were interested in finding routes to new compounds allied to methadone and benzomorphans, as well as to recently described basic indans, chromans, and tetralins.[16-18] Thus, a primary concern was to develop a useful method for synthesis of new 1-tetralones carrying a ketone group, and preferably also a phenyl substituent, at position 4. Reaction of 1,1-diphenylacetone with acrylonitrile[19] and with methyl acrylate gave **1a** and **1b**, respectively (Scheme I). Since cyclic group interactions[19] frequently occur in such compounds, it was necessary to explore various reactions of **1** in order to gain a clear idea of the best way to proceed toward tetralones. Nitrile **1a** with lithium aluminum hydride gave amino alcohol **2**. The action of sulfuric acid on **1a** was to give the corresponding ketamide **1c** and then enamine lactam **3**. This type of acid-promoted, δ-ketonitrile cyclization (*via* ketamide) has been observed in other cases.[20-22] It may also occur under basic conditions,[23] and is analogous to the formation of glutarimides from similar dinitriles and ester nitriles.[12,24] Evidence for structure **3** was first obtained by comparison of **3** with cyclic enamide **10**, prepared by hydrogenolysis of the vinylogous imide **9** as described by Koelsch;[25] the characteristic principal infrared bands (centered at 6.01 μ) of **3** and **10** corresponded almost exactly. Facile hydrogenation of **3** to lactam **4**, subsequent N-methylation to **5**, and finally lithium aluminum hydride reduction of **5** to the diphenyl piperidine **6**[26] gave additional evidence confirming structure **3**. Because of these results, and the earlier observed formation of 1,3-diketones as by-products in sulfuric acid hydrolysis of δ-ketonitriles to δ-keto acids,[27] it was advisable to use a method avoiding sulfuric acid for hydrolysis of **1a**. Refluxing **1a** or **1b** with hydrochloric–acetic acids gave a good yield of keto acid **7** without appreciable formation of by-products. Again, in cyclizing keto acid **7** to tetralone **8**,[15] one had to avoid such competitive group interactions as enol lactone or 1,3-diketone formation,[27] and some helpful information was obtained by studying at the same time the related closure of keto acid **11**. It had been observed that formation of a corresponding enol lactone from **11** with thionyl chloride[28] was responsible for failure of attempted aluminum chloride

SCHEME I



(15) W. Herz and G. Caple, *J. Org. Chem.*, **29**, 1691 (1964).

(16) H. E. Zaugg, R. W. DeNet, and E. T. Kimura, *J. Med. Pharm. Chem.*, **5**, 430 (1962); H. E. Zaugg and R. J. Michaels, *J. Org. Chem.*, **28**, 1801 (1963); **31**, 1332 (1966).

(17) A. A. Patchett and F. Giarrusso, *J. Med. Pharm. Chem.*, **4**, 385 (1961); G. deStevens, A. Halamandaris, P. Strachan, E. Donoghue, L. Dorfman, and C. F. Huebner, *J. Med. Chem.*, **6**, 357 (1963).

(18) (a) J. A. Barltrop, R. M. Acheson, P. G. Philpott, K. E. MacPhee, and J. S. Hunt, *J. Chem. Soc.*, 2928 (1956), and earlier papers; (b) J. F. Cavalla, J. P. Marshall, and R. A. Selway, *J. Med. Chem.*, **7**, 716 (1964); (c) S. Allison, J. Büchi, and W. Michaelis, *Helv. Chim. Acta*, **49**, 891 (1966).

(19) E. J. Cragoe, A. M. Pietruszkiewicz, and C. M. Robb, *J. Org. Chem.*, **23**, 971 (1958). The well-known preferences for anion delocalization of phenylacetones in the direction of the phenyl group has been made even clearer through recent studies by H. O. House and V. Kramar, *ibid.*, **28**, 3362 (1963).

(20) C. F. Koelsch and H. M. Walker, *J. Am. Chem. Soc.*, **72**, 346 (1950).

(21) A. I. Myers and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 1435 (1964); J. J. Vill, T. R. Steadman, and J. J. Godfrey, *ibid.*, **29**, 2780 (1964).

(22) Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanaoka, *Tetrahedron Letters*, 2261 (1965).

(23) A. D. Campbell and I. D. R. Stevens, *J. Chem. Soc.*, 959 (1956).

(24) E. Tagmann, E. Sury, and K. Hofmann, *Helv. Chim. Acta*, **35**, 1235, 1541 (1952); K. Hofmann, J. Kebrle, and H. J. Schmid, *ibid.*, **40**, 387 (1957); F. Salmon-Legagneur and C. Neveu, *Compt. Rend.*, **234**, 1060 (1952); *Bull. Soc. Chim. France*, 70 (1953).

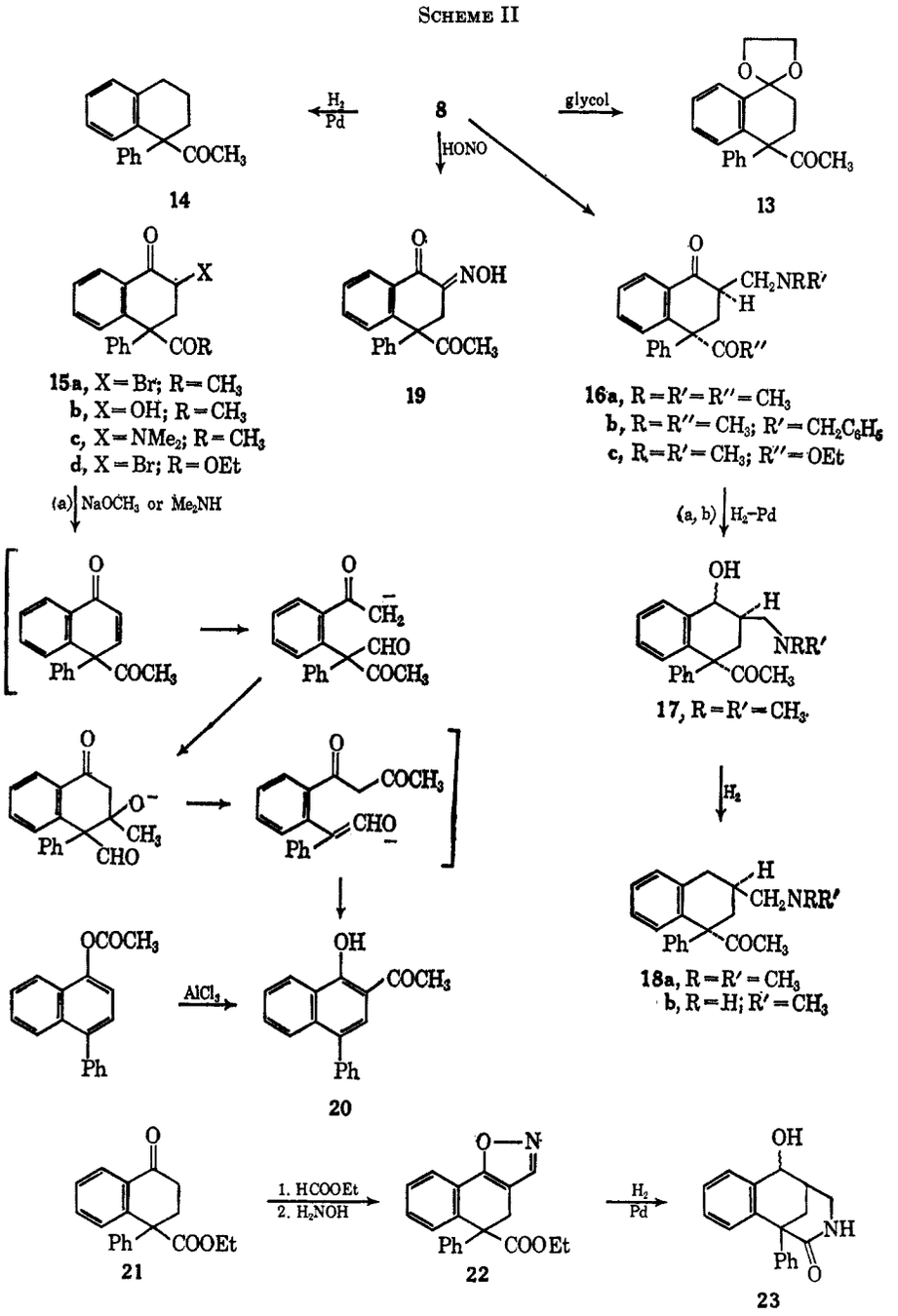
(25) C. F. Koelsch and D. L. Ostercamp, *J. Org. Chem.*, **26**, 1104 (1961).

(26) *Cf.* H. Kugita and T. Oine, *Chem. Pharm. Bull.* (Tokyo), **11**, 253 (1963); C. F. Koelsch, *J. Am. Chem. Soc.*, **65**, 437, 2093, 2458, 2459 (1943); N. F. Albertson, *ibid.*, **72**, 2594 (1950); R. K. Hill, C. E. Glassick, and L. J. Fliedner, *ibid.*, **81**, 737 (1959), for better known syntheses of piperidines by reductive closure of ketonitriles.

(27) E. J. Cragoe and A. M. Pietrnszkiew, *J. Org. Chem.*, **22**, 1338 (1957). Still worse for the purpose of hydrolysis are bases; *cf.* E. D Bergmann and J. Szmuszkovicz, *J. Am. Chem.*, **75**, 3226 (1953); and J. Colonge and R. Vuillemet, *Bull. Soc. Chim. France*, 1757 (1961).

(28) W. E. Bachmann and E. J. Fornefeld, *J. Am. Chem. Soc.*, **73**, 51 (1951). Compound **11** has been prepared by both routes indicated; see W. E. Bachmann and L. B. Wick, *ibid.*, **72**, 3388 (1950), and D. Elad and D. Ginsburg, *J. Chem. Soc.*, 2664, 4137 (1953). No difficulty is encountered in cyclizing to spiro-4-substituted 1-tetralones after reduction of the keto group in **11** and similar compounds; see T. Oh-Tshi, *J. Pharm. Soc. Japan*, **85**, 382 (1965).

SCHEME II



cyclization of **11** to **12**. A similar situation is present in **7**. The difficulty is circumvented easily by using concentrated sulfuric acid to cyclize **11** and **7** directly to tetralones **12** and **8**, respectively,[29] although control of the temperature (40°) is necessary to avoid excessive sulfonation.

The next phase of the work (Scheme II) consisted of examining characteristic reactions of **8** with the purpose of getting necessary evidence for structure. Initially it was thought that it might also be possible to develop some alternative routes from **8** to 2,4-bridged bicyclic amines in addition to those already found.[2,4] Diketone **8** formed a mono-2,4-dinitrophenylhydrazone, the infrared spectrum of which showed the methyl ketone group still present at position 4, indicating the hindered nature of the 4-acetyl group. In the same vein, glycol ketalization was selective, leading to **13**. Hydrogenolysis of **8** gave monoketone **14**, as expected for a 1-tetralone. Bromination of **8** took place quantitatively, giving a mixture of two diastereoisomeric 2-bromo compounds (**15a**) which were separated easily by fractional crystallization. However, reactions aimed at introducing a basic side chain or its precursor at position 2 of **8** were less successful. Mannich condensations of **8** with formaldehyde and the hydrochlorides of dimethylamine and methylbenzylamine under usual conditions resulted in low conversions to compounds **16a** and **b**, respectively. This contrasts with the ease of Mannich condensations in the case of 4-phenyl-1-tetralone itself.[30] Similarly, acid-catalyzed nitrosation of **8** gave a very low yield of **19**, an observa-

(29) G. N. Walker [*J. Am. Chem. Soc.*, **79**, 1772 (1957); **80**, 645 (1958)] described other carbonylium ion cyclizations in which enol lactones may intervene temporarily. After the present work was complete, preparation of the acid chloride from **7** using oxalyl chloride and cyclization to **8** with aluminum chloride were reported.[15]

(30) S. Wawzonek and J. Kozikowsky, *ibid.*, **76**, 1641 (1954).

tion in keeping with the poor results of earlier[2a] nitrosation of 4-carboethoxymethyl-4-phenyl-1-tetralone. Attempted 2-formylation of **8** gave in part a neutral hydroxy ketone believed to be the ketol resulting from reaction of the acetyl methyl group with the 1-tetralone (for evidence, see the Experimental Section), in contrast with the smooth 2-acylation of simpler 1-tetralones.[31] The results in **8** → **16** and **8** → **19** perhaps are best rationalized on the basis that position 2 of **8** is hindered sterically by both of the groups at position 4. Models indeed show that in either conformation of compound **8**, one of the 4 substituents is axial and fairly close to position 2. The idea of preparing 2,4-bridged heterocyclic compounds from **8** was abandoned in view of further information obtained as follows. Reduction of **19** gave no well-characterized product. Hydrogenations of Mannich bases **16** in the presence of palladium–charcoal were found to proceed more slowly than **8** → **14**, as is the case in other, similar 2-substituted tetralones,[2] and in one case could be done in two stages. After hydrogenating **16a** hydrochloride with Pd–C in ethanol under mild conditions, ketocarbinolamine **17** was obtained. More prolonged and vigorous reduction of compounds **16a** and **b** gave amino ketones **18**. As expected, debenzylation accompanied the hydrogenolysis of **16b**, giving **18b**. If the 2 and 4 substituents were properly oriented in this compound, one would anticipate cyclic enamine formation. Since no evidence was obtained to indicate such cyclic interaction, compounds **16**, **17**, and **18** probably have the *trans*-2-(aminomethyl)4-acetyl stereochemistry shown. The effects leading to introduction of a 2-(aminomethyl) group on the phenyl side of the molecule during Mannich condensation probably are not simply steric ones, since the phenyl group might be expected to block position 2 more effectively than would the acetyl group, and thus there may be repulsion between the two parallel dipoles of the attacking species (>C=N) and 4-(>C=O) group during that reaction. Mannich condensation of keto ester **21** with formaldehyde and dimethylamine hydrochloride similarly gave **16c**. The assigned stereochemical arrangement shown in **16c** could not be proven since no Mannich product was obtained from **21** using N-methylbenzylamine.

The peculiarities of compound **8** and its relatives were made even more apparent by a novel rearrangement which was found to take place with bromo diketone **15a**. When either of the isomeric 2-bromo compounds was treated with cold solutions of dimethylamine, or with other anhydrous bases such as sodium methoxide, the principal product was neither the 2-dimethylamino diketone[30] **15c** nor the $\Delta^{2,3}$-enedione.[32] Instead there was formed, presumably *via* enone reverse aldol reaction and ketol reclosure as shown in Scheme II, the rearrangement product, 2-acetyl-4-phenyl-1-naphthol **20**. This was proven by preparing an identical sample of **20** independently, through Fries rearrangement of 1-acetoxy-4-phenylnaphthalene.[33]

The facile, base-catalyzed rearrangement of **15a** or a corresponding unstable enedione to **20** is an interesting addendum to the well-known, acid-catalyzed rearrangement of 4,4-disubstituted 1,4-dihydronaphthalen-1-ones to 3,4-disubstituted 1-naphthols,[34] and contrasts markedly with the behavior of bromo ester **15d** and related bromamides[4] which undergo no such rearrangement.

Relevant study of the reduction of isoxazole **22** may be mentioned at this point. In contrast with **8**, keto ester **21** reacted smoothly with ethyl formate ($NaOCH_3$) to give the 2-hydroxymethylene keto ester and, following the well-known method,[31,35] this was converted to **22**. After hydrogenation of **22** in the presence of Pd–C in acetic acid, a low yield of the hydroxy bridged lactam **23** was isolated.[36] This approach to tetralin lactams similar to bridged chroman lactams[16] is therefore feasible, and moreover the **22** → **23** reduction was an encouraging, early indication that in tetralins of this type a catalytic reduction process is capable of generating an amino group oriented in part *cis* to a 4-functional group with which it may then interact to form a bridged ring.

Next investigated (Scheme III) were reductions of oximes from **8** and related diketones. Depending on the length of time of reaction of diketone **8** with hydroxylamine, either the monoxime **24a** or the dioxime **24b** could be prepared from **8**, again showing the hindered nature of the 4-$COCH_3$ group. Lithium aluminum hydride reduction[37] of **24a** in ether gave oximinocarbinol **25**, and, thus, this method was not suitable for generating a 1-amino group. However, palladium-catalyzed hydrogenation of **24a** at 60° led to formation of a mixture of basic products. The first component of this mixture to crystallize and lend itself to isolation and characterization was the bicyclic imine **27a**. Two additional products were obtained (as hydrochlorides) from the material remaining after separation of **27a**: first, the nonbicyclic, and thus evidently *trans*, 1-amino-4-acetyl compound **26**, and, second, the bicyclic secondary amine **28a**, formed by further reduction of **27a**, and side reactions of these kinds were found in subsequent work to be more or less inevitable. Better results were obtained in hydrogenation (palladium) of the dioxime **24b** under nearly the same conditions: **27a** was formed in better yield than in the monooxime hydrogenation, especially if a small amount of water was present. Ammonia was also generated during **24b** hydrogenation, but, since the oxime of ketone **14** was not reduced at all in the pres-

(31) W. S. Johnson and W. E. Shelberg, *J. Am. Chem. Soc.*, **67**, 1745, 1754 (1945).

(32) See E. C. Horning and R. U. Schock, *ibid.*, **70**, 2941 (1948). For various other α-bromo ketone transformations, see also C. L. Stevens and C. T. Lenk, *J. Org. Chem.*, **19**, 538 (1954); K. G. Rutherford and C. L. Stevens, *J. Am. Chem. Soc.*, **77**, 3278 (1955); C. L. Stevens, *et al.*, *J. Org. Chem.*, **31**, 2593 (1966); ref 18c.

(33) W. S. Johnson and A. Goldman, *ibid.*, **67**, 430 (1945); W. S. Borsche, *Ann.*, **526**, 1 (1936).

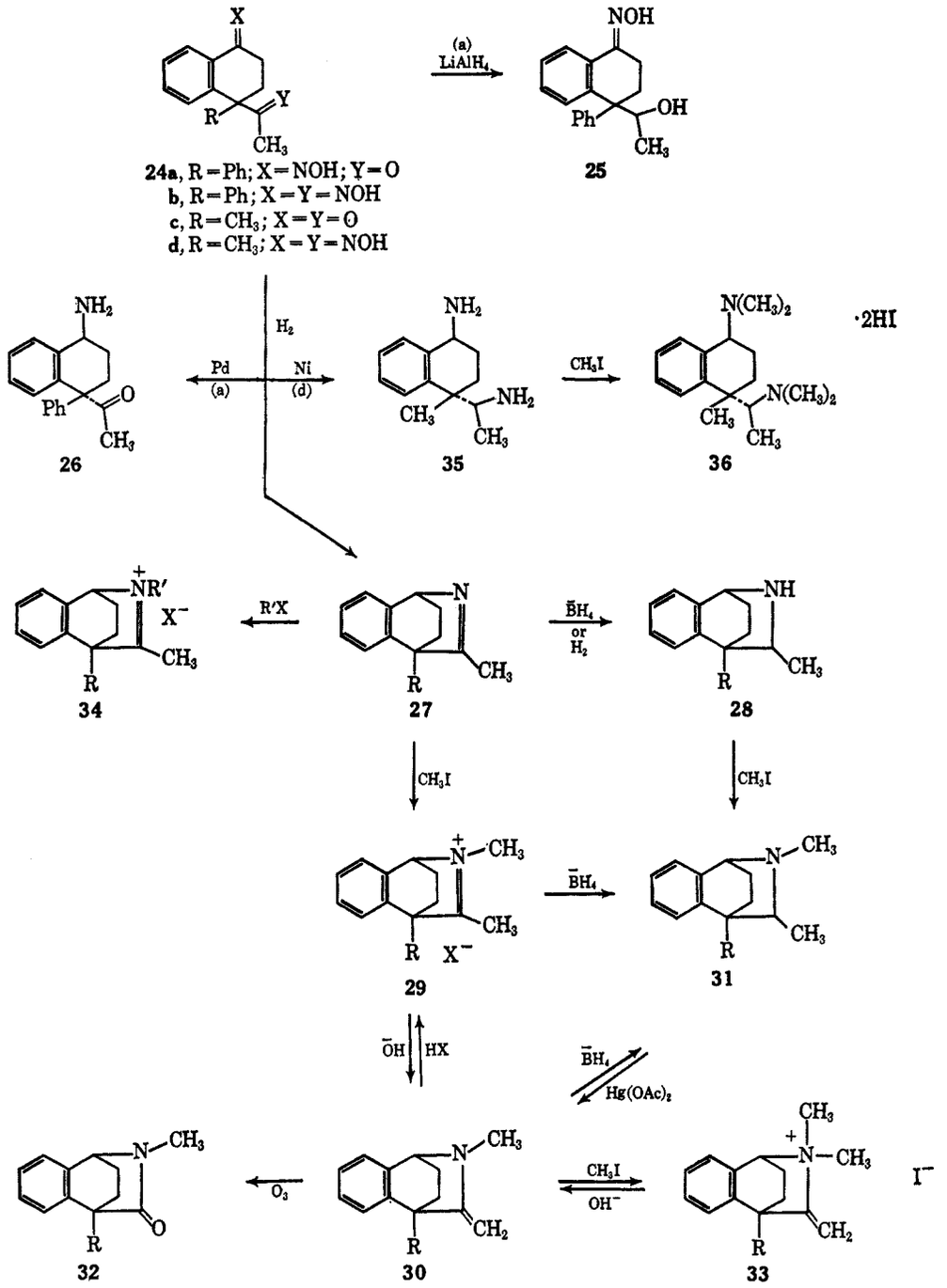
(34) R. T. Arnold, J. S. Buckley, and J. Richter, *J. Am. Chem. Soc.*, **69**, 2322 (1947); R. T. Arnold and J. S. Buckley, *ibid.*, **71**, 1781 (1949); R. T. Arnold, J. S. Buckley, and R. M. Dodson, *ibid.*, **72**, 3153 (1950).

(35) W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *ibid.*, **69**, 2942 (1947).

(36) From this crude reduction product there was also isolated noncrystalline, neutral material which probably arose from hydrogenolytic cleavage of a 2-(aminomethylene)-1-tetralone, as is known to occur in hydrogenation of other vinylogous amides; see G. N. Walker, *J. Org. Chem.*, **27**, 4227 (1962); J. C. Martin, K. R. Barton, P. G. Gott, and R. H. Meen, *ibid.*, **31**, 943 (1966), and references therein.

(37) J. L. Pinkus and T. Cohen [*ibid.*, **27**, 4356 (1962)] have reviewed methods for reduction of oximes. See also M. Freifelder, W. D. Smart, and G. R. Stone, *ibid.*, **27**, 2209 (1962); E. Breitner, E. Roginski, and P. N. Rylander, *ibid.*, **24**, 1855 (1959); *J. Chem. Soc.*, 2918 (1959); and C. F. Koelsch, *ibid.*, **26**, 1291 (1961), for oxime reduction, and also ref 18a and the following for preparation of indan and tetralin amines: J. v. Braun, O. Braunsdorf, and G. Kirschbaum, *Ber.*, **55**, 3648 (1922); A. G. Green and F. M. Rowe, *J. Chem. Soc.*, 955 (1918); C. F. Huebner, *et al.*, *J. Org. Chem.*, **27**, 4465 (1962); W. J. Rosen and M. J. Green, *ibid.*, **28**, 2797 (1963).

SCHEME III

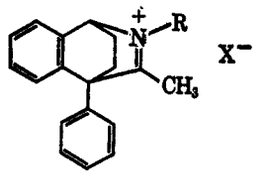


27 to 33a, R=phenyl
b, R=CH_3

ence of palladium, it was evident that ammonia arose during **24b** hydrogenation from reduction of the hydroxylamine which was formed by interaction of the 1-amino group and the 4-ketoximino group, rather than through any appreciable hydrogenolysis of the 1-aminotetralin. As by-product in the hydrogenation of **24b** there was isolated again compound **28a**, and nearly all the starting material was accounted for in the form of these basic products. All evidence obtained in hydrogenations of compounds **24** indicates that interaction of a generated 1-amino group with a *cis*-keto or ketoximino group at position 4 is aided sterically and takes place far more readily than does sterically unassisted ketimine formation.[38] Inspection of the quite rigid but unstrained Dreiding model of **27** serves to bear out this assumption. Apparently steric factors not only aid spontaneous bridged ring closure in these cases, but also prevent appreciable hydrogenolysis of 1-aminotetralins in the angular phenyl ketones and bicyclic compounds. Palladium normally leads to benzylamine hydrogenolysis and in fact for this reason was not useful in reduction of related 4-carboalkoxy oximes discussed elsewhere.

(38) R. W. Layer [*Chem. Rev.*, **63**, 489 (1963)] has reviewed ketimine chemistry.

TABLE I



R	X	Mp, °C dec	Recrystn solvent[a]	Infrared, >C=N⁺<, λ_{max}^{Nujol}, μ	Ultraviolet inflection, λ_{max}^{EtOH}, mμ (ε)	Formula	Calcd, % C	H	N	Found, % C	H	N
Ethyl	I	207–209	B	6.06	259 (430)	$C_{20}H_{22}IN$	59.56	5.50	3.45	59.26	5.77	3.26
n-Butyl	I	210–212	A	6.05	257 (990)	$C_{22}H_{26}IN$	61.25	6.08	3.25	60.97	6.08	3.10
Allyl	I	208–210	C	6.1–6.16	257 (1070)	$C_{21}H_{22}IN$	60.73	5.34	3.37	60.58	5.40	3.31
Benzyl	Cl	231–233	D	6.09	...	$C_{25}H_{24}ClN \cdot {}^1/_2H_2O$	78.41	6.58	3.66	78.50	6.56	3.70
$CH_2CH_2C_6H_5$	I	215–216	D	6.08	...	$C_{26}H_{26}IN$	65.13	5.47	2.92	64.97	5.55	2.82
$CH_2COOC_2H_5$	Br	186–187	E	(5.71), 6.09	258 (1050)	$C_{22}H_{24}BrNO_2$	63.77	5.84	3.38	64.03	5.92	3.25
$CH_2COOC_2H_5$	Cl	184–185	E	(5.75), 6.07 6.12	257 (1010)	$C_{22}H_{24}ClNO_2 \cdot {}^1/_2H_2O$	69.6	6.65	3.7	69.14	6.92	3.72

[a] A, acetone; B, acetone–ether; C, benzene; D, acetone–methanol; E, ethanol–ether.

Structures of the bicyclic bases isolated from reduction of compounds **24a** and **b** were confirmed in several ways. Sodium borohydride reduction of imine **27a**, gave **28a**, identical with material obtained by hydrogenation of **27a**. By quaternization[39] of imine **27** with primary alkyl halides, a series of 4-phenyl-N-alkyliminium salts was prepared (Table I), including the N-methyliminium iodide **29a** (X = I^-), reactions of which were studied further. On treating **29a** with base, there was obtained the crystalline enamine **30a**. This enamine was reconverted typically[40] to **29a** iodide, bromide, chloride, and other salts by treatment with appropriate acids. Both the iminium salts **29a** and the enamine **30a** were reduced with borohydride to the N-methyl bicyclic amine **31a**, and the latter characteristically was reoxidized to **30a** by mercuric acetate,[40b,f] although in low yield. The methylenamine **30a** in addition was ozonized to N-methyllactam **32a**, identical with a sample synthesized independently, as described in another connection.

Study of the various reactions of diketone **8** thus served to uncover a rather unique class of compounds integrally incorporating the currently interesting enamine ⇄ iminium moiety as part of a bicyclic system. It was then of interest to extend the synthesis of compounds **27** through **31a** to the analogous bridged imines and enamines having a methyl group at position 4. Therefore 3-phenyl-2-butanone[41] was cyanoethylated,[19] the ketonitrile was hydrolyzed as in **1a** → **7**, and the resulting δ-keto acid[19] was cyclized with sulfuric acid, as in synthesis of **8**, to the diketone **24c**. This compound did not have as hindered a 4-acetyl group as did **8**, and although it formed a 1-mono-2,4-dinitrophenylhydrazone the monooxime could not be prepared. Hydrogenation of the corresponding dioxime **24d** in the presence of palladium or nickel was more difficult to control than that of **24b**, and gave mixtures of bases which were more difficult to separate than those obtained from **24a** and **b**. Eventually, suitable conditions for the reduction were found, and four compounds were isolated from the mixtures. If hydrogenation of **24d** in the presence of Pd–C at room temperature was interrupted after uptake of somewhat more than 2 moles of hydrogen, imine **27b** could be isolated as the corresponding hydrochloride from the crude basic fraction. More prolonged Pd–C hydrogenation led to formation of bicyclic secondary amine **28b**, which could be removed from the crude material as hydrochloride or converted with methyl iodide to the more easily isolated hydroiodide of tertiary bicyclic amine **31b**. When **24d** was reduced in the presence of Raney nickel, there was less selectivity in attack on the oximino groups, and at least partial formation of compound **35**; treatment of the mixture with methyl iodide gave the bisdimethylamino hydroiodide **36**.

As in the case of **27a**, quaternization of imine **27b** with methyl iodide and benzyl bromide gave respective bicyclic iminium salts **29b** (X = I) and **34** (R′ = benzyl, X = Br), which could be converted to respective enamines and thence to other iminium halides. Reduction of **27b** again served to substantiate the structures.

The basicity of enamine **30a** (pK_a = 9.9 in water, 9.5 in 80% Cellosolve–20% water) was found to be greater than that of the corresponding tertiary amine **31a** (pK_a = 7.6) and that of the corresponding secondary amine **28a** (pK_a = 8.4). These results are consistent with the accepted view that cyclic enamines are more basic than corresponding saturated, tertiary amines,[42] and do not support a recent contention to the contrary,[40g] based on pK_a measurements of some 1-amino-1-isobutenes. It was also observed that compounds **30** are not easily C-alkylated. Treatment of

(39) H. Decker and P. Becker, *Ann.*, **395**, 328, 362 (1913).

(40) (a) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954); (b) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *ibid.*, **77**, 439 (1955); (c) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963); (d) N. L. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *ibid.*, **28**, 1499 (1963); (e) N. J. Leonard and A. G. Cook, *ibid.*, **81**, 5627 (1959); (f) M. G. Reinecke and L. R. Kray, *ibid.*, **29**, 1736 (1964); **31**, 4215 (1966); (g) E. J. Stamhuis, W. Maas, and H. Wynberg, *ibid.*, **30**, 2156, 2160 (1965); (h) *cf.* C. A. Grob, A. Kaiser, and E. Renk, *Chem. Ind.* (London), 598 (1957); *Helv. Chim. Acta*, **40**, 2170 (1957), for Δ²-quinuclideines which lack true enamine character since prototropic shift of bridged enamine is sterically impossible; it would be of interest to examine 2-alkylidenequinuclidines since they may be expected to have more olefinic character than normal enamines; (i) for earlier enamine–iminium⁺ transformations in isoquinolines, see, *inter alia*, E. E. P. Hamilton and R. Robinson, *J. Chem. Soc.*, 1029 (1916); J. B. Koepfli and W. H. Perkin, *ibid.*, 2989 (1928); S. N. Chakravarti, R. D. Haworth, and W. H. Perkin, *ibid.*, 2275 (1927); J. L. Bills and C. R. Noller, *J. Am. Chem. Soc.*, **70**, 957 (1948); R. Robinson, *J. Chem. Soc.*, 1029, 1038 (1916); B. Witkop, *J. Am. Chem. Soc.*, **77**, 6592 (1955).

(41) E. M. Schultz, J. B. Bicking, S. Mickey, and F. S. Crossley, *ibid.*, **75**, 1072 (1953); G. Darzens, *Compt. Rend.*, **141**, 768 (1947).

(42) R. Adams and J. E. Mahan, *J. Am. Chem. Soc.*, **64**, 2588 (1942).

30a with methyl iodide under mild conditions gave the crystalline N,N-dimethylenaminium iodide **33a** rather than a 3-ethyliminium salt; compounds **33** reverted to **29** when boiled with alcohols or a solution of methyl iodide in ethanol, and to enamines **30** when treated with bases. This behavior parallels the N-alkylation of $\Delta^{1,10}$-dehydroquinolizidines.[40f] At present, we believe that there may be a correlation between relative basicity of enamines and the ease with which they are C-alkylated. Thus, the less basic Δ^1-alkenylamines,[40g] in which steric effects do not prevent electron delocalization, tend to function as ambident carbanions in displacements,[43] while many cyclic enamines in which prototropic shift occurs within a ring appear to behave more like ordinary tertiary amines, having high electron density on nitrogen, high basicity, and alkylating mainly on the nitrogen.

Experimental Section[44]

4,4-Diphenyl-5-ketohexanoic Acid and Derivatives. Nitrile 1a.—After treatment of a solution of 210 g (1 mole) of 1,1-diphenylacetone and 30 ml of 40% Triton B methoxide in 500 ml of tetrahydrofuran with 53 g of acrylonitrile in 100 ml of tetrahydrofuran at 25–30° during 2 hr, acidification at ice temperature, and treatment with ice and water, the crude product was collected, pressed free of oily material, and triturated with ether–methanol, to give 124 g (47%) of colorless crystals: mp 117–118° (lit.[19] mp 113–115°); λ_{max}^{Nujol} 4.41, 5.88 μ.

Ester 1b was prepared by similar reaction of 105 g of 1,1-diphenylacetone with 51.5 ml of methyl acrylate in 200 ml of *t*-butyl alcohol and 200 ml of tetrahydrofuran, catalyzed by the addition of 15 ml of 40° Triton B methoxide at room temperature (1.5 hr), followed by 0.75 hr heating on a steam cone. After standing overnight the solution was acidified at 0° and diluted with water. The oil was extracted with ether, and the ether solution was washed with several portions of water and dried. Evaporation of the ether gave oily, crude keto ester[19] suitable for hydrolysis to the acid. Acid **7** was obtained by the two following methods.

A.—Hydrolysis of 130 g of ketonitrile **1a** with 800 ml of glacial acetic acid and 800 ml of concentrated hydrochloric acid (refluxed for 5 hr). After distillation *in vacuo*, the suspension was treated with 3 l. of ice and water. The crude acid (137 g, 99%) had mp 138–140° (lit.[19] mp 137.5–139°). Recrystallization from ethanol or methanol raised the melting point to 140.5–142.5°, λ_{max}^{Nujol} 5.87 μ.

B.—Hydrolysis of crude keto ester **1b** by 1.5 hr of reflux with a solution of 800 ml of 5% aqueous potassium hydroxide and 100 ml of methanol, followed by acidification gave 68 g (48% from diphenylacetone) of acid, mp 135–140°, suitable for use in further reactions. A sample, recrystallized from ethanol, had mp 140–141° and was identical with the acid obtained in A.

4,4-Diphenyl-5-hydroxy-1-aminohexane (2).—A mixture of 9 g of lithium aluminum hydride, 1 l. of tetrahydrofuran, and 11.7 g of ketonitrile **1a** was refluxed and stirred for 7 hr. After cautious hydrolysis with 30 ml of water and filtration, the crude base was isolated by evaporation of the tetrahydrofuran and trituration with ether, yielding 11.0 g of colorless acid-soluble crystals, mp 75–81°. Recrystallization from ether gave 7.9 g of pure material: mp 135–137°; λ_{max}^{Nujol} 2.96 μ, and bonded NH bands.

Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 79.95; H, 8.89; N, 5.21.

4,4-Diphenyl-5-ketohexanoamide (1c).—Nitrile **1a** (6.5 g) was treated with 60 g of concentrated sulfuric acid while moderating the exothermic effect. After standing for 0.5 hr the purple solution was poured over ice. The gummy, yellow solid was extracted with ethyl acetate, and the organic solution was washed with successive portions of sodium bicarbonate solution and water, dried ($MgSO_4$), and evaporated. The viscous residue crystallized on standing overnight. From cyclohexane–ethyl acetate was obtained 1.5 g of colorless crystals: mp 98–105°, raised on further recrystallization from the same solvents to 112.5–114°; λ_{max}^{Nujol} 2.90, 2.94, 3.03, 3.20 (series of broad bands), 5.88–6.02–6.19 μ (triplet).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.53; H, 6.80; N, 4.88.

5,5-Diphenyl-6-methylene-2-piperidone (3).—Nitrile **1a** (39.5 g) was treated with 350 ml of concentrated sulfuric acid without cooling, and the solution was allowed to stand for 1.5 hr. After pouring over ice, the resulting viscous, yellow material was isolated by decanting the aqueous solution, and was washed with water and ethanol. The crude material was dissolved in 200 ml of boiling ethanol and the solution was allowed to stand and crystallize overnight. The product (10.0 g of colorless crystals, mp 250–253°), after recrystallization from ethanol, had mp 251–253°; bonded NH at *ca.* λ_{max}^{Nujol} 3.13, and intense, shouldered peak at 6.01 μ; λ_{max}^{EtOH} 233 mμ (ϵ 15,520) with shoulder at 225 mμ (ϵ 18,020); nmr D_2O exchangeable NH, no CH_3, and $=CH_2$ at δ 3.3 (broad singlet).

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.08; H, 6.68; N, 5.25.

The same compound, as well as amide **1c**, apparently was obtained by exposure of 5.7 g of nitrile **1a** to a hot solution of 10 g of KOH in 80 ml of ethanol for 2 hr. Partial hydrolysis occurred, as evidenced by ammonia evolution. The base-insoluble material (1.2 g) present after dilution with water was recrystallized from ethanol to give 1.2 g of **3**: mp 252–255°; λ_{max}^{Nujol} 2.91, 3.02, 3.13, 6.08 μ; evidently contaminated with amide or other substance.

Anal. Found: C, 79.52; H, 6.52; N, 5.09.

From the aqueous solution in the same experiment there was isolated by acidification a compound, mp 197–198° after ethanol recrystallization (λ_{max}^{Nujol} 3.05–3.07, 6.18 μ) which appeared from spectra and analysis to be **4,4-diphenyl-1,3-cyclohexanedione**. The material gave a weak, greenish ferric chloride test.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.66; H, 6.23.

5,5-Diphenyl-6-methyl-2-piperidone (4).—A suspension of 10.0 g of compound **3** and 4 g of 10% Pd–C in 300 ml of glacial acetic acid was shaken under 45 psi of hydrogen at 75° for 2.5 hr. The uptake of 1 molar equiv (3-psi pressure drop in a 4-l. system) was complete in 1 hr. Evaporation of the filtered solution gave a viscous, yellow oil which crystallized in the presence of ether and afforded 7.3 g (72%) of colorless material, mp 215–217°. Recrystallization from ethyl acetate gave a pure sample: mp 218–220°; λ_{max}^{Nujol} 3.13, 6.02 μ; λ_{max}^{EtOH} 263 mμ (ϵ 470).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.40; H, 7.31; N, 5.44.

5,5-Diphenyl-1,6-dimethyl-2-piperidone (5).—Compound **4** (4.8 g) and 1.5 g of 56% sodium hydride–mineral oil in 500 ml of toluene were warmed for 15 min under reflux. Methyl iodide (10 ml) was added, and the mixture was stirred and refluxed for 8 hr. After treating the cooled mixture with water, the organic phase was diluted with ether, washed with water, dried ($MgSO_4$), and evaporated. The residue with ether gave 4.8 g of colorless crystals: mp 157–159° (not raised on recrystallization from ether or methanol); broad peak at λ_{max}^{Nujol} 6.15 with shoulders at 6.01–6.06, 6.23 μ; λ_{max}^{EtOH} 259, 263, 269 mμ (ϵ 500, 510, 410, respectively).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 82.13; H, 7.58; N, 5.07.

3,3-Diphenyl-1,2-dimethylpiperidine (6).—A mixture of 3.2 g of lactam **5**, 800 ml of tetrahydrofuran, and 6 g of lithium aluminum hydride was stirred and refluxed for 4 hr. After hydrolysis of the cooled suspension with 38 ml of water, filtration, and evaporation of the solution, the crude base was dissolved in ether and allowed to crystallize at ice temperature. There was obtained 2 g of colorless crystals, mp 94–96°. Recrystallization from ethanol afforded a pure sample, mp 94–96°, spectrally devoid of NH or carbonyl bands.

Anal. Calcd for $C_{19}H_{23}N$: C, 85.98; H, 8.74; N, 5.28. Found: C, 85.83; H, 8.79; N, 5.24.

(43) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954); G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963); G. Opitz, H. Mildenberger, and H. Suhr, *Ann.*, **649**, 47 (1961).

(44) Melting points were obtained using a stirred, Thomas–Hoover silicone oil bath. Infrared spectra were measured in the Perkin-Elmer double-beam instrument, and ultraviolet curves were obtained using a Beckman recording spectrophotometer. Unless otherwise noted, samples for analysis were dried at 80° (0.05 mm) and pK_a values were obtained by potentiometric titration in 80% ethylene glycol monomethyl ether (20% water solution). Proton magnetic resonance spectra were obtained using Varian A-60 Mc apparatus with tetramethylsilane as internal standard.

The picrate, as yellow crystals from ethanol, had mp 220.5–222°.

Anal. Calcd for $C_{25}H_{26}N_4O_7$: C, 60.72; H, 5.30; N, 11.33. Found: C, 61.07; H, 5.52; N, 11.42.

4a-Phenyl Δ^8-octahydro-2-quinolone (10).—Compound **9** (19 g; mp 238–240°; λ_{max}^{Nujol} 3.12, 5.87, 6.10 μ), prepared as described earlier,[20] was hydrogenolyzed in the presence of 7 g of 10% Pd–C in 350 ml of ethanol at 45 psi and 50° following, with slight modifications, the procedure described earlier.[25] Absorption of 2 molar equiv of hydrogen (13.5 psi pressure drop in a 4-l. system) took place in 0.5 hr. Filtration, evaporation of the solvent, and recrystallization of the residue from ethyl acetate gave 7.5 g of colorless crystals: mp 211–216° (raised on further recrystallization from ethyl acetate to mp 215–217.5°); bonded NH and peak at λ_{max}^{Nujol} 6.01 with shoulders at 5.96 and 6.17–6.23 μ; λ_{max}^{EtOH} 230 mμ (ϵ 13,610); nmr D_2O exchangeable NH, δ 9.6, CH triplet centered at 5.3 (lit.[25] mp 211–214°).

Spiro[2-cyclohexanone-1,4′(1′)-tetralone] (12). **A.**—Compound **11** was prepared by hydrolysis of either the cyanoethylation product of 2-phenylcyclohexanone[28] or the octahydroquinolone **10**[25] with 15 parts (by weight) each of glacial acetic acid and concentrated hydrochloric acid, and refluxing for 4.5 hr, which in each case gave a nearly quantitative yield of colorless crystals: mp 113–115°, λ_{max}^{Nujol} 5.88 μ (unresolved doublet).

B.—Compound **11** (8.7 g) was dissolved in 90 ml of concentrated H_2SO_4, and the solution was allowed to stand for 3 days at room temperature. The solution was poured over ice. The neutral fraction, isolated by extraction with ether, washed with successive portions of 3% sodium hydroxide solution and water, dried ($MgSO_4$), and evaporated, crystallized in ether and gave 3.7 g of crystals: mp 94–95°; λ_{max}^{Nujol} 5.90, 5.99 μ; λ_{max}^{EtOH} 248, 290 mμ (ϵ 11,150, 1670, respectively).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.12; H, 7.13.

The **bis-2,4-dinitrophenylhydrazone** was recrystallized from ethyl acetate as red crystals: mp 243–245° dec; λ_{max}^{Nujol} 6.16, 6.26 μ.

Anal. Calcd for $C_{27}H_{24}N_8O_8$: C, 55.10; H, 4.11; N, 19.04. Found: C, 55.20; H, 4.19; N, 18.75.

The corresponding **monooxime**, 4′-oximinospiro[2-cyclohexanone 1,1′-tetralin], separated after a few minutes of heating: mp 232–234° (after recrystallization from ethanol); λ_{max}^{Nujol} 3.05, 5.94 μ; λ_{max}^{EtOH} 249, 293 mμ (ϵ 11,500, 1800, respectively).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.05; H, 7.07; N, 5.92.

4-Acetyl-4-phenyl-1-tetralone (8).—To 800 ml of concentrated sulfuric acid there was added 95 g of acid **7** with stirring, over a period of 1.5 hr, keeping the temperature at 30–40°. The deep red solution was stirred at room temperature for 4–5 hr and poured over 4 kg of chopped ice. After extraction with ether, the organic solution was washed with dilute sodium hydroxide solution and water, dried ($MgSO_4$), and evaporated to a small volume, and the crystals were collected: 44 g (50%); mp 106–108° (not raised on further recrystallization from ether) (lit.[15] mp 99–101°, from cyclization of the acid chloride corresponding to **8** with aluminum chloride); λ_{max}^{Nujol} 5.85, 5.96 μ (lit.[15] 5.88, 5.94 μ; λ_{max}^{EtOH} 249, 291–294 mμ (ϵ 11, 190, 2010, respectively); nmr ($CDCl_3$) CH_3 at δ 2.18 (singlet, three protons), CH_2 at 2.6 (much fine splitting, four protons), eight aromatic protons in a very complex multiplet centered at 7.25, 8 H at 8.2 (one proton, multiplet).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.89; H, 6.23.

The **1-mono-2,4-dinitrophenylhydrazone** separated from ethanol when the derivative was prepared in the usual way using sulfuric acid, and was recrystallized from ethanol–ethyl acetate as red crystals: mp 201.5–203.5°; λ_{max}^{Nujol} 5.82, 6.13, 6.25 μ.

Anal. Calcd for $C_{24}H_{20}N_4O_5$: C, 64.86; H, 4.54; N, 12.61. Found: C, 64.68; H, 4.54; N, 12.77.

Compound 13 was prepared by refluxing for 4.5 hr under a water trap a solution of 5 g of diketone **8**, 4.7 g of ethylene glycol, and 0.3 ml of benzene sulfonic acid in 50 ml of benzene. The neutral product was fractionally recrystallized from ether yielding 0.8 g of material, mp 136–147°, which after further recrystallization from ether afforded colorless crystals: mp 155–156, λ_{max}^{Nujol} 5.86 μ.

Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.64; H, 6.71.

Dioxime 24b.—Diketone **8** (26.4 g) in 400 ml of ethanol was treated with a solution prepared at 0° from 26 g of hydroxylamine hydrochloride in 200 ml of water and 26 g of sodium hydroxide in 200 ml of water. The solution was refluxed for 3.5 hr, cooled, adjusted to pH 7.5 by adding dilute hydrochloric acid, then chilled to 0°. The crystals were collected, washed with water, and air dried. The yield of dioxime, mp 219–222°, was 28.1 g (95%). Recrystallization from ethanol gave a sample: mp 221–222°; λ_{max}^{EtOH} 256 mμ (ϵ 12,910) with inflection at 297 mμ (ϵ 800); λ_{max}^{Nujol} 6.08, 6.24, with broad, intense hydroxyl band at 3.03–3.13 μ.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.58; H, 6.17; N, 9.34.

Monooxime 24a.—Reaction of 20 g of diketone **8** with hydroxylamine, carried out as in the preceding experiment except that the solution was refluxed for 10 min, gave as the first crop of crystals (16.5 g) of **24a**, mp 163–167°. Further recrystallization from ethanol gave a pure sample: mp 171–172°; λ_{max}^{Nujol} 3.00 (broad, intense), 5.89 (intense), 6.15–6.23 μ (weak, sharp doublet); λ_{max}^{EtOH} 257 mμ (ϵ 12,590), with weak inflection at 299 mμ.

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.13; H, 6.11; N, 5.04.

The second crop of crystals (2.3 g, mp 185–205°) was mainly **dioxime 24b**; further recrystallization from ethanol gave a sample, mp 221–222°, identical with material obtained as described above.

2-Isonitroso-4-acetyl-4-phenyl-1-tetralone (19).—Diketone **8** (3.0 g) in 100 ml each of benzene and ether was saturated with hydrogen chloride, treated at 0° with 1.2 g of butyl nitrite, and allowed to stand at 0–15° for 2 hr. After treatment with ice and water, the crude product, isolated from the sodium bicarbonate—washed, dried organic layer by evaporation, was kept at 0° for several days until it partly crystallized. With the aid of ether there was obtained *ca.* 0.3 g of light orange crystals, mp 166–168° dec. Recrystallization from cyclohexane–ethyl acetate gave a pure sample: mp 180.5–182.5°; λ_{max}^{Nujol} 3.13 (broad), 5.88, 6.20–6.26 μ; λ_{max}^{EtOH} 272 mμ (ϵ 13,960); red ferric chloride test.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 74.13; H, 5.18; N, 4.74.

1-Acetyl-1-phenyltetralin (14).—Hydrogenation of 2.8 g of diketone **8** in 300 ml of ethanol in the presence of 1.0 g of 10% Pd–C at 50 psi and room temperature for 3 hr, and recrystallization of the crude product from ether, gave crystals: mp 68–71°, λ_{max}^{Nujol} 5.86 μ, benzene bands in ultraviolet. The same compound was obtained in nearly quantitative yield when the hydrogenation was carried out on 20 g of diketone in acetic acid at room temperature with 10 g of the same catalyst.

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.32; H, 7.22.

The corresponding **oxime** had mp 203–206° after recrystallization from ethanol; λ_{max}^{Nujol} 3.04–3.06, 6.05–6.25 μ; λ_{max}^{EtOH} 265, 274 mμ (ϵ 530, 370, respectively).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.28; H, 7.38; N, 5.30.

This oxime was not affected by hydrogen in the presence of 10% Pd–C in ethanol or acetic acid.

2-Bromo-4-acetyl-4-phenyl-1-tetralone (15a).—Bromine (11.6 g, 0.0725 mole) in 100 ml of benzene was added (20 min) to a stirred solution of 18.8 g (0.0712 mole) of diketone **8** in 500 ml of benzene. After washing with several portions each of sodium bicarbonate solution and water, the organic layer was dried ($MgSO_4$), filtered, and evaporated. The crude product was allowed to crystallize in the presence of ether. The first crop consisted of the *cis*-2-bromo-4-acetyl isomer (9.8 g of crystals): mp 114–116° (recrystallization from ether raised the melting point to 116–118°); λ_{max}^{Nujol} 5.88 with shoulder at 6.01 μ; λ_{max}^{EtOH} 254, 299 mμ (ϵ 11,310, 2560, respectively).

Anal. Calcd for $C_{18}H_{15}BrO_2$: C, 62.99; H, 4.41; Br, 23.29. Found: C, 62.43; H, 4.54; Br, 23.33.

The mother liquor on standing in the presence of ethyl acetate crystallized. Trituration with ether afforded the second product (*trans*-2-bromo-4-acetyl isomer) as 3.5 g of crystals: mp 131–134° (after recrystallization from ethyl acetate, raised on further recrystallization from the same solvent to 135.5–137°); λ_{max}^{Nujol} 5.89, with shoulder at 5.96 μ; λ_{max}^{EtOH} 253, 290 mμ (ϵ 8880, 1920, respectively), with inflection at 302 mμ (ϵ 1690).

Anal. Calcd for $C_{18}H_{15}BrO_2$: C, 62.99; H, 4.41; Br, 23.29. Found: C, 62.73; H, 4.46; Br, 23.21.

The nmr spectra ($CDCl_3$) of the two bromo diketones confirmed the structural assignments: the C-2 proton in the *trans* diastereoisomer is not deshielded by 4-phenyl (δ = 4.53 ppm), whereas the C-2 proton in the *cis* isomer is deshielded (centered at δ =

5.22 ppm). Furthermore, there is slight deshielding of the 4-acetyl methyl group by the benzo ring in the *trans* isomer (δ = 2.23 ppm) in contrast with the lack of such deshielding in the *cis* isomer (δ = 2.17 ppm).

2-Bromo-4-carbethoxy-4-phenyl-1-tetralone (15d).—Similar reaction of 10.0 g of 4-carboethoxy-4-phenyl-1-tetralone[1] with 5.75 g of bromine gave a crude product which crystallized partly after standing 2 months. The crystalline isomer (3.4 g), isolated with the aid of methanol, and recrystallized from the same solvent, had mp 91–92°; λ_{max}^{Nujol} 5.78–5.87 μ; λ_{max}^{EtOH} 251, 294 mμ (ϵ 12,190, 2400, respectively).

Anal. Calcd for $C_{19}H_{17}BrO_3$: C, 61.14; H, 4.59; Br, 21.41. Found: C, 61.41; H, 4.59; Br, 20.98

2-Acetyl-4-phenyl-1-naphthol (20). A. From Rearrangement of 15a in the Presence of Dimethylamine.—Compound **15a** (5.5 g, a mixture of isomers) was treated with 75 ml of 10% dimethylamine in toluene at 0° for 30 hr. After filtration to remove dimethylamine hydrobromide, the solution was evaporated *in vacuo*. The yellow residue crystallized on standing at 0° in the presence of ether, giving 1.1 g of yellow crystals: mp 182–184° (not raised on recrystallization from methanol); blue-green ferric chloride test; λ_{max}^{Nujol} 6.17 (shoulder at 6.23), 6.34 μ, together with broad bands indicating chelation; λ_{max}^{EtOH} 219, 260, 299, 375 mμ (ϵ 31,500, 34,200, 5400, 6000, respectively); in dilute NaOH solution, λ_{max} 257, 281, 337, 399 mμ (ϵ 20,700, 23,720, 9650, 12,960, respectively).

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.43; H, 5.36.

B. From 15a with Sodium Methoxide.—Treatment of 5.2 g of **15a** with a solution of 1.8 g of sodium in 180 ml of methanol gave an orange solution; after standing overnight, most of the methanol was removed *in vacuo*, the residue was treated with water, and the product was extracted with ether. Evaporation of the washed and dried ether solution gave 2 g of yellow, viscous oil which crystallized in the presence of ether and afforded yellow crystals: mp 182–183°; mixture melting point with sample from A undepressed; spectra identical.

From the aqueous alkaline layer, by acidification with HCl and extraction with ether, there was isolated another product, evidently **2-hydroxy-4-acetyl-4-phenyl-1-tetralone (15b)** as 0.5 g of crystals: mp 153–154° (after trituration with ether and recrystallization from methanol); bonded OH band, sharp doublet at λ_{max}^{Nujol} 5.83 and 5.91 μ; λ_{max}^{EtOH} 245, 291 mμ (ϵ 12,590, 2520, respectively).

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.01; H, 6.05.

C. Fries Rearrangement.—1-Acetoxy-4-phenylnaphthalene[33] (7 g) was treated with 7 g of anhydrous aluminum chloride, and after exothermic reaction was complete the mixture was heated on a steam cone for 15 min with stirring. The cooled melt was hydrolyzed with ice and dilute hydrochloric acid and extracted with ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated. The residue crystallized readily in methanol giving 1.4 g of yellow crystals: mp 182–184°; mixture melting point with samples from A and B undepressed; spectra identical.

2-(N,N-Dimethylaminomethyl)-4-acetyl-4-phenyl-1-tetralone (16a).—A mixture of 5.4 g of diketone **8**, 3.9 g of dimethylamine hydrochloride, 3.5 g of paraformaldehyde, 100 ml of ethanol, and 1 drop of concentrated hydrochloric acid was refluxed for 16 hr. The solvent was evaporated and the cooled residue was treated with 200 ml of water. The ether-washed solution was made basic by adding a slight excess of dilute sodium hydroxide solution. The base was extracted with ether. The ether solution was washed twice with water, dried (K_2CO_3), and evaporated. The crude product crystallized slowly, giving 1.7 g of colorless crystals: mp 114–116°; λ_{max}^{Nujol} 5.94 (shoulder at 6.03), 6.23 μ; λ_{max}^{EtOH} 249, 293 mμ (ϵ 10,710, 2240, respectively), with inflection at 301 mμ (ϵ 10,410).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.41; H, 7.31; N, 4.45.

The corresponding hydrochloride was recrystallized from ethanol–ether as colorless crystals: mp 164–167°; λ_{max}^{Nujol} 3.84, 4.00, 5.89, 6.25 μ; λ_{max}^{EtOH} 251, 292 mμ (ϵ 11,610, 1800, respectively).

Anal. Calcd for $C_{21}H_{23}NO_2 \cdot HCl$: C, 70.48; H, 6.76; N, 3.91. Found: C, 70.11; H, 6.75; N, 3.83.

Similar condensation of 5.3 g of diketone **8** with 9.5 g of benzylmethylamine hydrochloride and 3.6 g of paraformaldehyde in 100 ml of ethanol in the presence of 1 drop of concentrated hydrochloric acid (refluxed for 6 hr) gave 1.7 g of crude compound **16b** as 0.5 g of crystals from ether: mp 124–125°; λ_{max}^{Nujol} 5.85, 5.92 μ (doublet); λ_{max}^{EtOH} 249, 292 mμ (ϵ 10,750, 2170, respectively).

Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.77; H, 6.72; N, 3.49.

1 Hydroxy-2-(N,N-dimethylaminomethyl)-4-acetyl-4-phenyltetralin Hydrochloride (17a).—A solution of 1.7 g of **16a** in 200 ml of ethanol and 1.5 ml of 6 *N* ethanolic hydrogen chloride, together with 1.4 g of 10% Pd–C in 10 ml of water, was shaken under hydrogen (40 psi) at 60° for 1 hr. A pressure drop of 0.8 psi (4-l. system) took place in a few minutes. After evaporation of the filtered solution and trituration with ether, recrystallization from ethanol–ether gave crystals: mp 203–205°; λ_{max}^{Nujol} 2.88, 3.02, 3.76 (broad), 5.87 μ; λ_{max}^{EtOH} 259, 265, 298 mμ (ϵ 450, 440, 340, respectively), with points of inflection at 253, 269, 275, 291, 308 mμ.

Anal. Calcd for $C_{21}H_{25}NO_2 \cdot HCl$: C, 70.08; H, 7.28; N, 3.89. Found: C, 69.95; H, 7.18; N, 3.93.

The corresponding free base could not be obtained in crystalline form.

2-(N,N-Dimethylaminomethyl)-4-acetyl-4-phenyltetralin Hydrochloride (18a).—Hydrogenation of **16a** (3.3 g), in 300 ml of ethanol and 5.5 ml of 6 *N* ethanolic HCl in the presence of 1 g of 20% Pd–C was carried out at 70° under 45 psi of hydrogen for 5 hr. Evaporation of the filtered solution gave glassy material which crystallized after standing for 1 week. Trituration with ether–ethanol afforded 3.0 g of colorless crystals: mp 187–192° (raised on further recrystallization from the same solvents to 193–195°); λ_{max}^{Nujol} 5.87 μ and broad ionic bands; λ_{max}^{EtOH} 260, 265, 275 mμ (ϵ 534, 526, 392, respectively), with inflections at 252, 307 and a plateau at 289–300 mμ (ϵ 376).

Anal. Calcd for $C_{21}H_{25}NO \cdot HCl$: C, 73.34; H, 7.62; N, 4.07. Found: C, 73.37; H, 7.63; N, 4.14.

2-(N-Methylaminomethyl)-4-acetyl-4-phenyltetralin (18b).—A solution of 0.5 g of **16b** in 200 ml of ethanol and 1.2 ml of 6 *N* ethanolic HCl was shaken with 0.5 g of 10% Pd–C under 50 psi of hydrogen at 70° for 3 hr. After evaporation of the filtered solution, the residue was triturated with ether containing a small amount of methanol, to give 0.2 g of grayish crystals, mp 203–206°. Recrystallization from ethanol–ether gave a pure sample of the **hydrochloride** as colorless crystals: mp 209–211°; λ_{max}^{Nujol} 5.84, broad bands at 3.65, 4.41 μ; λ_{max}^{EtOH} 260, 266, 277, 299 mμ (ϵ 550, 530, 390, 360, respectively), with inflections at 254, 269, 310 mμ.

Anal. Calcd for $C_{20}H_{23}NO \cdot HCl$: C, 72.83; H, 7.33; N, 4.25. Found: C, 72.40; H, 7.20; N, 4.21.

The same compound was obtained by hydrogenolysis of **16b** in glacial acetic acid in the presence of 10% Pd–C at 70°.

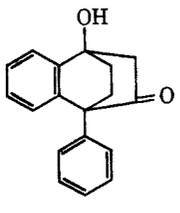
2-(N,N-Dimethylaminomethyl)-4-carboethoxy-4-phenyl-1-tetralone Hydrochloride (16c).—Reaction of 2.6 g of 4-carboethoxy-4-phenyl-1-tetralone[2] with 2.0 g of dimethylamine hydrochloride and 2.4 g of paraformaldehyde, carried out as for **16a**, gave 1.0 g of crude, basic product (an oil) which was converted to the hygroscopic hydrochloride as colorless crystals from ethanol–ether: mp 149.5–151.5°; λ_{max}^{Nujol} 4.13, 5.78, 5.89 μ; λ_{max}^{EtOH} 250, 294 mμ (ϵ 12,600, 2280, respectively).

Anal. Calcd for $C_{22}H_{25}NO_3 \cdot HCl$: C, 68.12; H, 6.76; N, 3.61. Found: C, 67.89; H, 7.05; N, 3.60.

Attempted Formylation of Diketone 8.—Reaction of 2.5 g of **8** with 0.25 g of dry sodium methoxide and 6 ml of ethyl formate in 75 ml each of ether and benzene at room temperature for 24 hr gave 1.1 g of a crude enol as viscous, red oil giving a red ferric chloride test. This material could not be characterized further. From the neutral fraction with the acid of ether there was isolated 0.5 g of crystals: mp 244–248° (raised on further recrystallization to 248–250°); λ_{max}^{Nujol} 2.87 (intense), 5.85 μ; λ_{max}^{EtOH} 257 mμ (ϵ 700).

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.76; H, 5.93.

The results are rationalized by the following structure[45] for the hydroxy ketone.



(45) *Cf.* K. Morita and T. Kobayashi, *J. Org. Chem.*, **31**, 229, 3106 (1966).

A correctly integrating nmr spectrum in agreement with this structure was obtained (DMSO solvent): OH at δ 5.95, disappearing on D_2O treatment, no methyl signal, CH_2 multiplets centered at 2.23, 2.55, shielded aromatic proton signals at 6.43 and 6.6, a complex pattern of aromatic protons at 6.8–7.6.

2-Hydroxymethylene-4-carboethoxy-4-phenyl-1-tetralone.—To dry sodium methoxide prepared from 1.3 g of sodium was added a solution of 14.7 g of 4-carboethoxy-4-phenyl-1-tetralone and 15 ml of ethyl formate in 350 ml of dry benzene. The suspension was stirred at room temperature 2–3 hr, and allowed to stand overnight. The sodium salt was collected, washed with dry ether, and dissolved in water, the aqueous solution was acidified with hydrochloric acid, and the enol was extracted with ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated. The crude, oily product (*ca.* 8 g) gave a strong ferric chloride test, and was used directly in the next step.

5-Carboethoxy-4,5-dihydro-5 phenylnaphtho[1,2-*d*]isoxazole (22).—The crude enol from the preceding experiment and 15 g of hydroxylamine hydrochloride in 300 ml of acetic acid were refluxed for 10 min. After addition of water (300 ml) to the cooled solution, the oil was extracted with ether. The ether solution was washed with dilute sodium hydroxide solution and water, dried ($MgSO_4$), and evaporated. The product crystallized slowly in the presence of methanol. Recrystallization from ether afforded 7.0 g of crystals: mp 80–85° (raised on further recrystallization to mp 94.5–95.5°); λ_{max}^{Nujol} 5.80 (intense), 5.89, 6.09, 6.25 μ; λ_{max}^{EtOH} 283 mμ (ϵ 13,510), with inflections at 222, 303 mμ (ϵ 16,780, 6740, respectively).

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.33; H, 5.39; N, 4.33.

1-Hydroxy-2-aminomethyl-4-phenyltetralin-4-carboxylic Acid Lactam (23).—Hydrogenation (50 psi) of 3.5 g of **22** in 200 ml of glacial acetic acid in the presence of 3.5 g of 10% Pd–C at 70° for 6 hr, followed by filtration of the catalyst and evaporation, gave crude material which was shaken with ether and dilute sodium hydroxide solution. The organic layer was separated, washed with water and dilute HCl, dried ($MgSO_4$), filtered, and evaporated. The oily residue (*ca.* 3 g) crystallized partly when taken up in 100 ml of ether. The crystals (0.35 g) were collected and washed with ether: mp 235–239°, raised after several recrystallizations from methanol–ether to 241–243°; λ_{max}^{Nujol} 3.11 (intense, broad), 5.99–6.05 μ (intense).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.69; H, 6.23; N, 4.97.

The remaining, neutral material (infrared ester band) could not be obtained in crystalline form. From the aqueous, acid wash there was obtained, after addition of sodium hydroxide solution 0.2 of the same hydroxylactam.

1-Oximino-4-(1-hydroxyethyl)-4-phenyltetralin (25).—Mono oxime **24a** (5 g) in 250 ml of tetrahydrofuran was added to 4 g of lithium aluminum hydride in 750 ml of ether; after refluxing and stirring for 10 hr, the mixture was hydrolyzed by slow addition of 20 ml of water. After filtration, drying ($MgSO_4$), and evaporation of the solvents, trituration of the residue with ether gave 2.6 g of crystals, mp 179–183°. Recrystallization from aqueous ethanol afforded material: mp 184–186°; λ_{max}^{Nujol} 3.10–3.20 (intense, broad), 6.13, 6.24 μ; λ_{max}^{EtOH} 255 mμ (ϵ 12,640) with inflection at 298 mμ (ϵ 760).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.91; H, 6.89; N, 5.21.

3-Methyl-4-phenyl-1,4-dihydro-1,4-ethanoisoquinoline (27a).
A. From Reduction of Ketooxime 24a.—A solution of 2.8 g of **24a** in 300 ml of ethanol, with 1.0 g of 10% Pd–C, was shaken under 50 psi of hydrogen at 60° for 3 hr. After filtration of the catalyst and evaporation of the solvent, the crude material was taken up in ether. The ether solution was dried ($MgSO_4$) and evaporated. The crude, basic product crystallized partly after standing at 0° overnight. Filtration with the aid of ether gave 1.0 g of crystals, mp 86–98°. Recrystallization from ethanol–ether and then from aqueous ethanol gave a pure sample as colorless crystals: mp 135–136°; λ_{max}^{Nujol} 6.12 μ (intense); λ_{max}^{EtOH} 258, 264 mμ (ϵ 620, 470, respectively); nmr ($CDCl_3$) CH_3 at δ 1.85 (singlet), H_1 at 5.52, aromatic proton signals at 6.7–7.5.

Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.28, 87.54; H, 6.90; N, 5.62; pK_a = 4.1.

The corresponding hydrochloride was prepared using ethanolic HCl and ether and was recrystallized from ethanol–ether: mp 223–225°; λ_{max}^{Nujol} 5.99, broad $H^+N=$ bands at 5.0–5.3 μ; λ_{max}^{EtOH} 257 mμ (ϵ 690) with inflections at 250, 264 mμ.

Anal. Calcd for $C_{18}H_{18}ClN$: C, 76.18; H, 6.39; N, 4.93. Found: C, 76.23; H, 6.50; N, 4.97.

The corresponding picrate was recrystallized from ethanol as bright yellow, gleaming flakes: mp 211.5–213.5, λ_{max}^{Nujol} 6.13–6.18 μ (doublet).

Anal. Calcd for $C_{24}H_{20}N_4O_7$: C, 60.50; H, 4.23; N, 11.76. Found: C, 60.32; H, 4.30; N, 11.58.

Treatment of the remaining crude basic material (*ca.* 1.8 g) with alcoholic HCl gave a crude hydrochloride, which was fractionally crystallized from acetone. The first two crops were **1-amino-4-acetyl-4-phenyltetralin hydrochloride (26)**: mp 239–241°; λ_{max}^{Nujol} 2.86 (broad), 5.86 μ in addition to broad ionic bands; λ_{max}^{EtOH} 264, 296 mμ (ϵ 540, 215, respectively).

Anal. Calcd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.92; H, 6.78; N, 4.60.

The remaining, crude hydrochloride upon recrystallization from acetone–methanol afforded a pure sample of **3-methyl-4-phenyl-1,2,3,4-tetrahydro-1,4-ethanoisoquinoline hydrochloride (28a) hydrochloride**, mp 300–302°, spectrally devoid of bands owing to unsaturated groups other than phenyl and identical with a sample obtained *via* borohydride reduction of **27a**, as described below.

Anal. Calcd for $C_{18}H_{20}ClN$: C, 75.64; H, 7.05; Cl, 12.41; N, 4.90. Found: C, 75.84; H, 7.03; Cl, 12.32; N, 4.88.

B. Reduction of Dioxime 24b.—Hydrogenation of a solution of 30 g of dioxime **24b** in 250 ml of ethanol and 1 g of water in the presence of 7.5 g of 10% Pd–C at 60° for 5.5 hr resulted in a pressure drop of 24.5 psi in 3 hr (4-l. system). A strong odor of ammonia was noticed upon releasing the pressure. Evaporation of the filtered solution gave crude material to which *ca.* 150 ml of ether was added. The crystals were collected and were washed with a small amount of ether. The crude product (18.1 g) was dissolved in boiling ether, and the ether solution was filtered to remove an insoluble residue (4.2 g, mp *ca.* 274° dec; not characterized precisely but appearing to be partly an aminooxime; infrared 2.99, 6.17 μ). The ether solution, upon concentration to a smaller volume, deposited 14.4 g of crystalline **imine 27a**: mp 128–134°, raised on further recrystallization from ether to 135–136°; λ_{max}^{Nujol} 6.13 μ; identical with sample obtained by reduction of **24a**. The highest yield of **27a** observed in repeating this experiment was 17.8 g (70.5%).

Hydrogenations of **24b** carried out without adding water were slower, gave lower yields of imine, and led to formation of **28a** as well. Treatment of remaining crude base fraction with methyl iodide gave crystalline methiodide **29a**, indicating the presence of a small amount of additional **27a** in the mixture.

3-Methyl-4-phenyl-1,2,3,4-tetrahydro-1,4-ethanoisoquinoline (28a).—A solution of 4.0 g of **27a** in 200 ml of methanol was treated with 15 g of sodium borohydride, in portions. The solution was refluxed for 2 hr, evaporated to a smaller volume, and treated with water. The crude amine was collected, washed with water, and air dried to give 1.2 g of colorless crystals, mp 170–172°. Recrystallization from ether afforded solvated crystals, mp 178–179° (after drying *in vacuo* at 100°, mp 180–181°).

Anal. Calcd for $C_{18}H_{19}N \cdot 0.5H_2O$: C, 83.68; H, 7.80; N, 5.42. Found: C, 84.11; H, 7.92; N, 5.42; pK_a = 8.4.

The corresponding **N-acetyl** derivative was prepared by refluxing a sample of the base with excess acetic anhydride for 2 hr. Recrystallization from ether gave colorless crystals: mp 174–176°, λ_{max}^{Nujol} 6.10 μ.

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.40; H, 7.40; N, 5.10.

The corresponding **hydrochloride**, recrystallized from ethanol, had mp 298–301° and was identical with **28a** hydrochloride obtained as by-product in the preceding hydrogenation experiments: mmp 298–300°; infrared spectra were identical.

2,3-Dimethyl-4-phenyl-1,4-dihydro-1,4-ethanoisoquinolinium Iodide (29a, X = I).—A solution of 30 g of mine **27a** in 350 ml of ethanol was treated with 140 ml of iodomethane and refluxed for 4 hr. The yield was 42.2 g (85%) of methiodide **monohydrate** as colorless crystals: 245–247° dec (after recrystallization from methanol); λ_{max}^{Nujol} 2.81–2.90 (broad), 6.03 μ (sharp); inflections at λ_{max}^{EtOH} 257, 263 mμ (ϵ 950, 820, respectively), and high end absorption.

Anal. Calcd for $C_{19}H_{20}IN \cdot H_2O$: C, 56.02; H, 5.45; I, 31.2; N, 3.42. Found: C, 55.65; H, 5.35; I, 32.3; N, 3.41.

Recrystallization from absolute ethanol and prolonged drying *in vacuo* gave anhydrous salt as colorless crystals, mp 239–240.5° dec, having negligible infrared hydroxyl band and a sharp peak at 6.04 μ.

Anal. Calcd for $C_{19}H_{20}IN$: C, 58.62; H, 5.18; N, 3.60. Found: C, 58.77; H, 5.24; N, 3.61.

Other quaternary immonium salts (Table I) were prepared from **27a** by a similar procedure, except that allyl iodide and the imine were warmed together in benzene for 15 min.

2-Methyl-3-methylene-4-phenyl-1,4-dihydro-1,4-ethanoisoquinoline (30a).—A solution of 39.2 g of iminium iodide from the preceding experiment in 500 ml of warm methanol was treated with excess 10% sodium hydroxide solution and the mixture was shaken with 1 l. of ether. The ether solution was separated, washed with two portions of water, dried (K_2CO_3), and filtered. Evaporation to a volume of 100–200 ml gave crystals which were collected and washed with a small quantity of ether. The yield of enamine as colorless crystals, mp 171–175°, was 24.8 g (99%, the purity was not improved by further recrystallization from ether): λ_{max}^{Nujol} 6.18–6.21 μ (unresolved enamine and phenyl doublet); inflection at λ_{max}^{EtOH} 228 mμ (ϵ 4670) in addition to high end absorption at 206 mμ (ϵ 23,000) and the usual benzene maxima; pK_a = 9.5; nmr ($CDCl_3$) =CH_2 at δ 3.29, 3.52 suppressed or disappearing on addition of D_2O or H^+, in addition to complex methylene multiplets at 1.6–2.4, H_1 at 4.23 (singlet), aromatic protons at 6.8–7.6, NCH_3 at 2.83.

Anal. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.37; H, 7.33; N, 5.30.

The pK_a, measured using a water solution of iminium chloride from the following experiment, was 9.9. The enamine was reconverted to iodide **29a** (X = I) on treatment with aqueous alcoholic hydriodic acid.

2,3-Dimethyl-4-phenyl-1,4-dihydro-1,4 ethanoisoquinolinium chloride (29a, X = Cl).—Enamine **30a**, on treatment with anhydrous HCl in benzene, ether, or ethanol–ether, gave a quantitative yield of colorless crystals, mp 242–244° dec. The samples were somewhat hygroscopic; spectra and analysis indicated a **monohydrate.**

Anal. Calcd for $C_{19}H_{20}ClN \cdot H_2O$: C, 72.25; H, 7.02; N, 4.44. Found: C, 71.75; H, 6.99; N, 4.43.

Upon equilibration with the atmosphere or recrystallization from slightly moist ethanol–ether, the stable **sesquihydrate** was obtained as colorless crystals: mp 242–243° dec; λ_{max}^{Nujol} broad 2.95, sharp 6.05 μ; inflections at λ_{max}^{MeOH} 208, 250 mμ (ϵ 19,000, 800, respectively); nmr (D_2O) 3-CH_3 at δ 2.66, NCH_3 at 4.27, H_1 at 6.29, in addition to hydroxyl (H_2O) at 5.10, aromatic protons at 7.1–8 ppm.

Anal. Calcd for $C_{19}H_{20}ClN \cdot 1.5H_2O$: C, 70.25; H, 7.14; N, 4.31. Found: C, 70.18; H, 7.04; N, 4.26.

The chloride was soluble in water, and was converted back into **30a** on treatment with sodium hydroxide solution. It was also prepared directly from iodide **29a** (X = I) as follows. A mixture of 1.5 g of the iodide, 5 g of freshly precipitated, washed AgCl, and 250 ml of methanol was stirred and refluxed for 4.5 hr and filtered, the filtrate was evaporated, and the residue was recrystallized from methanol–ether giving 1.2 g of crystals: mp 231–232° dec; infrared identical with above sample of sesquihydrate.

2,3-Dimethyl-4-phenyl-1,4-ethano-1,2,3,4-tetrahydroisoquinoline (31a).—Reduction of chloride or iodide **29a** or of enamine **30a** in methanol solution by excess sodium borohydride in each case heating under reflux for 2 hr then evaporating to smaller volume and adding water gave oil which crystallized on standing. The product was collected, washed with water, air dried, and recrystallized from ether to yield 3.7 g (from 6 g of iodide) of colorless crystals, mp 83–89°. Further recrystallization from ether gave a pure sample, mp 90–92°.

Anal. Calcd for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.33; H, 8.16; N, 5.27; pK_a = 7.6.

The corresponding **picrate** as yellow crystals from ethanol had mp 219.5–221°.

Anal. Calcd for $C_{25}H_{24}N_4O_7$: C, 60.97; H, 4.91; N, 11.38. Found: C, 61.05; H, 4.89; N, 11.12.

The corresponding **hydrochloride** was recrystallized from ethanol–ether as colorless crystals, mp 303.5–305°.

Anal. Calcd for $C_{19}H_{21}N \cdot HCl$: C, 76.11; H, 7.40; N, 4.67. Found: C, 76.16; H, 7.22; N, 4.74.

The corresponding **hydroiodide**, prepared by treating a sample of the base with a 10% solution of HI in ethanol and a small amount of water and recrystallized from methanol–ethanol, had mp 262–264°, spectrally devoid of C=N bands.

Anal. Calcd for $C_{19}H_{21}N \cdot HI$: C, 58.35; H, 5.67; N, 3.58. Found: C, 58.21; H, 6.19; N, 3.35.

The corresponding **methiodide** was prepared by refluxing 1 g of base with 18 ml of iodomethane and 200 ml of methanol for 6 hr. The residue, after evaporation of solvent and reagent, was triturated with ether and recrystallized from methanol as pale yellow crystals: mp 259–262° dec; spectra (infrared, 2.90 μ) and analysis indicated slight hydration.

Anal. Calcd for $C_{20}H_{24}IN$: C, 59.26; H, 5.97; N, 3.46. Found: C, 58.87; H, 6.19; N, 3.60.

Amine **31a** was also obtained (a) by hydrogenating 0.9 g of enamine **30a** in ethanol (200 ml) in the presence of 10% Pd–C (1.0 g) at room temperature for 3 hr; the product was identified as the hydrochloride (0.75 g), mp 300–303° dec, identical with the first sample; and (b) by methylation of **28a** with iodomethane, followed by conversion of crude hydroiodide to the base.

Oxidation of 31a to 30a.—A solution of 1 g of **31a** and 20 g of mercuric acetate in 100 ml of glacial acetic acid was refluxed for 3 hr and then heated at 100° for 2 days. After removing the acetic acid *in vacuo*, the cooled residue was taken up in water and made basic with 10% sodium hydroxide solution. The precipitate was collected, washed with water and ether, and digested with warm 7% hydrochloric acid. The acid solution was filtered and treated with a slight excess of sodium sulfide in small portions, and the mercury sulfide was removed by filtration. The cooled, acid solution was again made basic and the base was extracted with ether. The ether solution was washed with water, dried (K_2CO_3), and evaporated to a small volume (5–10 ml). The crude enamine which separated as yellow crystals was collected and washed with a small amount of ether: 100 mg, mp *ca.* 130–140°. There was not enough material for purification of the enamine, and an attempt to prepare the iodide gave a difficultly separated mixture of **29a** (X = I) and **31a** hydroiodide. Therefore the crude base was converted to **chloride 29a** (X = Cl) using a slight excess of ethanolic HCl in dry ether; after recrystallization from methanol–ether there were obtained colorless crystals: mp 239–240° dec, with **29a** chloride from preceding experiment mmp 240–243° dec (undepressed); infrared spectra identical.

2-Methyl-4-phenyl-1,4-ethano-1,2,3,4-tetrahydro-3-isoquinolone (32a).—Ozone was passed for 1.8 hr through a solution of 0.5 g of **30a** in 250 ml of ethyl acetate at room temperature. After standing overnight, the solution was treated with 75 ml of 10% hydrochloric acid and 5 g of zinc dust and allowed to stand for 20 min with occasional swirling. The organic solution was separated, washed with several portions of water, dried ($MgSO_4$), and evaporated; the odor of formaldehyde was apparent. The residue crystallized in ether giving 100 mg of discolored crystals, mp *ca.* 175°. Recrystallization from ethanol–ether gave a pure sample: mp 198–200°, λ_{max}^{Nujol} 6.01 μ, λ_{max}^{EtOH} 246 mμ (ϵ 410).

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.13; H, 6.47; N, 5.30.

2,2-Dimethyl-3-methylene-4-phenyl-1,4-ethano-1,2,3,4-tetrahydroisoquinolinium Iodide (33a).—Samples of enamine **30a** (1.0 g), on 10 min of reflux with iodomethane (10 ml) or on standing in ether solution with excess of the same reagent, gave in each case 0.2–0.3 g of ether-insoluble, slightly orange crystals, mp 240–245° dec (sintering from *ca.* 230°). The material was dissolved in ethanol without excessive heating, and the filtered solution was chilled or diluted with a small amount of ether. The recrystallized sample had mp 259–263° dec; λ_{max}^{Nujol} 2.89 (broad), 4.97 (moderate to weak iminium$^+$ band), 6.23 μ (weak); λ_{max}^{EtOH} 211, 258 mμ (ϵ 28,800, 600, respectively). The crystal form, alcohol solubility, and infrared spectrum were different from those of **29a** iodide.

Anal. Calcd for $C_{20}H_{24}INO \cdot H_2O$: C, 57.01; H, 5.74; N, 3.32. Found: C, 57.76; H, 6.04; N, 3.34.

On treatment of this salt with excess 10% aqueous sodium hydroxide solution and methanol, and isolation of the base there was obtained the enamine **30a**, mp 171.5–173.5°, identical with the authentic sample.

On boiling the salt with methanol for 0.5 hr there was obtained a sample of **29a** (X = I): mp 245–247° dec; infrared spectrum (2.86–2.92, 6.04 μ) the same as that of the previous sample.

2,3-Dimethyl-4-phenyl-1,4-dihydro-1,4-ethanoisoquinolinium Bromide (29a, X = Br).—A solution of enamine **30a** (0.3 g) in dry ether was treated with 2 ml of benzyl bromide. Separation of colorless precipitates was slow at room temperature, and rapid when the mixture was warmed gently on a steam cone (10 min). The finely divided salt was collected, washed with ether, and recrystallized from ethanol–ether as colorless crystals: mp 252–254° dec; λ_{max}^{Nujol} 2.96 (moderate broad), 6.05 μ (sharp); λ_{max}^{EtOH} inflections at 236, 264 mμ (ϵ 1320, 730, respectively). The sample proved to be a **hemihydrate.**

Anal. Calcd for $C_{19}H_{20}BrN \cdot 0.5H_2O$: C, 64.96; H, 6.03; N, 3.99. Found: C, 64.86; H, 6.25; N, 3.94.

The same compound was obtained by treatment of enamine **30a** with hydrogen bromide and recrystallization from ethanol.

4-Acetyl-4-methyl-1-tetralone (24c). A. Methylation of Phenyl-2-propanone.—Phenyl-2-propanone (122 g) in dry ether (400 ml) was added (15 min) to a stirred, ice-cold suspension of sodium methoxide (from 23 g of sodium) in 300 ml of dry ether. After 20 min, iodomethane (128 g) was added gradually (15 min) at 0°. The suspension was then allowed to warm slowly to room temperature and was stirred for 6 hr. After filtration, the ether solution was washed with water, dried ($MgSO_4$), and evaporated. The crude, oily ketone was used directly in the next step. A sample was converted to the **semicarbazone**, mp 175–176° after recrystallization from ethanol (lit.[41] mp 172–173°).

B. Cyanoethylation.—Crude, alkylated ketone from A was dissolved in 500 ml of tetrahydrofuran. The solution was cooled to 20° and treated first with 30 ml of 40% Triton B methoxide, then during 15 min with a solution of 47.6 g of acrylonitrile in 100 ml of tetrahydrofuran, keeping the temperature at 20–30° by means of external cooling as necessary. After 2 hr at room temperature the crude product was isolated as usual and hydrolyzed without further purification.

C. Hydrolysis.—Cyanoketone from B was refluxed for 3 hr with 1100 ml each of concentrated HCl and glacial acetic acid. The crude acid was isolated and distilled *in vacuo*, giving colorless oil, bp 174–176.5° (0.6 mm), [lit.[19] bp 171–174° (0.1 mm)], which crystallized. Recrystallization from ether afforded 100.3 g of keto acid, mp 70–72°. A pure sample (from ether) had mp 73–74°, λ_{max}^{Nujol} 5.83–5.92 μ.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.84; H, 7.44.

D. Cyclization.—The acid from C (25 g) was added to 500 ml of concentrated H_2SO_4, and after it had dissolved the solution was kept at room temperature overnight. After pouring over ice, extracting the organic material with ether, and separating neutral and acidic fractions, there was obtained 7 g of recovered acid and 14.4 g (63%) of diketone **24c** as a pale yellow oil. The material did not crystallize: λ_{max} 5.86, 5.93 μ, no monosubstituted phenyl peak.

The **mono-2,4-dinitrophenylhydrazone** was recrystallized from ethanol–ethyl acetate and then from ethyl acetate as red crystals: mp 193–195°; λ_{max}^{Nujol} 5.85, 6.14, 6.27 μ.

Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.75. Found: C, 59.83; H, 4.90

The **dioxime 24d**, was obtained by the usual method (15-min reflux) in quantitative yield. A sample, recrystallized from ethanol, had mp 224–226°; λ_{max}^{Nujol} 3.09, 6.08 μ; λ_{max}^{EtOH} 254, 297 mμ (ε 12,600, 990, respectively).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.07; H, 6.91; N, 12.05.

3,4-Dimethyl-1,4-dihydro-1,4-ethanoisoquinoline (27b).—A solution of 11.6 g of **24d** in 300 ml of ethanol containing 2.3 g of 5% Pd–C was shaken under 50 psi of hydrogen at room temperature for 4.2 hr, until a pressure drop of 9.1 psi (2.28 molar equiv) had occurred. After filtration and evaporation of the ethanol, the crude material was taken up in ether and filtered to remove 0.6 g of unreacted dioxime, mp 222–224°. The ether solution was extracted with several small portions of 10% hydrochloric acid. The acid solution was slowly made basic at ice temperature. The oil which separated was extracted with ether, and the ether solution was washed with several small portions of water, dried (K_2CO_3), and evaporated. The oily base (5 g) was dissolved in *n*-butyl alcohol–ethyl acetate and treated with a slight excess of hydrogen chloride. There was obtained 1.4 g (12%) of **27b hydrochloride**, mp *ca.* 220–233° dec. Recrystallization from methanol–ether gave colorless crystals: mp 234–235° (resolidifying and melting again at 298–301° dec); λ_{max}^{Nujol} 4.96, 5.28, 5.99, broad 4.07–4.3 μ; inflections at λ_{max}^{EtOH} 230, 259, 266 mμ (ε 1650, 580, 500, respectively).

Anal. Calcd for $C_{13}H_{15}N \cdot HCl$: C, 70.42; H, 7.27; Cl, 16.0; N, 6.32. Found: C, 70.70; H, 7.35; Cl, 16.3; N, 6.25.

When 10% Pd–C was employed in this reduction, little or no dioxime was recovered, but the yield of iminium salt isolated from the crude base was lowered, owing to over-reduction.

The hydrochloride was dissolved in a small amount of water and carefully made basic at ice temperature with 20% KOH solution. The base was collected and washed with small portions of ice water. Samples of hydrated **imine 27b**, dried at room temperature, had mp 50–53°; λ_{max}^{Nujol} 3.03, 6.12 μ; inflections at λ_{max}^{EtOH} 257, 263 mμ (ε 450, 390, respectively). After recrystallization from ether or from ethanol–water, and drying *in vacuo*, crystals, mp 38–39°, of anhydrous base were obtained. The sample became oily on standing exposed to air, but could be stored in a capped vial at 0°.

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.05; H, 8.22; N, 7.45.

2,3,4-Trimethyl-1,4-dihydro-1,4-ethanoisoquinolinium Iodide (29b, X = I).—The imine **27b** reacted readily with iodomethane; after a few minutes, ether was added and the salt was collected (quantitative yield) and recrystallized from ethanol–ether as colorless, hygroscopic crystals: mp 213–215° dec; λ_{max}^{Nujol} 6.06 μ; λ_{max}^{EtOH} 218 mμ (ε 16,570), inflection at 266 mμ (ε 690).

Anal. Calcd for $C_{14}H_{18}NI$: C, 51.39; H, 5.54; N, 4.28. Found: C, 51.43; H, 5.46; N, 4.28.

2-Benzyl-3,4-dimethyl-1,4-dihydro-1,4-ethanoisoquinolinium Salts.—Similar quaternization of imine **27b** with excess benzyl bromide in a small amount of ethanol by warming on a steam cone for 0.5 hr gave crystals of the **bromide**: mp 235–237° dec (from ether–ethanol), λ_{max}^{Nujol} 6.08 μ, λ_{max}^{EtOH} 224–231 mμ (ε 3450).

Anal. Calcd for $C_{20}H_{22}BrN$: C, 67.41; H, 6.23; N, 3.93. Found: C, 67.55; H, 6.22; N, 3.77.

The nmr spectrum (D_2O) gave 4- and 3-methyl signals centered δ 2.4 and 3.16, respectively, H_1 proton at 6.16, benzyl methylene at 5.75 (collapsed AB signal), and methylene multiplet at 1.8–2.6, as well as complex aromatic proton signals.

A sample of the bromide was treated with sodium hydroxide solution, and the base was extracted with ether. The ether solution was washed with water, dried (K_2CO_3), and evaporated without heating. The **enamine** was an oil which gradually turned yellow on exposure to air. It was converted to the iminium **iodide**, by treatment with a 15% aqueous ethanol solution of HI and recrystallization from ethanol: mp 215–216° dec; λ_{max}^{Nujol} 6.11 μ; λ_{max}^{MeOH} 207 mμ (ε 21,130), inflection at 220 mμ (ε 17,290).

Anal. Calcd for $C_{20}H_{22}IN$: C, 59.56; H, 5.50; N, 3.47. Found: C, 59.39; H, 5.45; N, 3.40.

3,4-Dimethyl-1,4-ethano-1,2,3,4-tetrahydroisoquinoline (28b) Hydrochloride.—Another hydrogenation of **24d** (2.5 g) was carried out in the presence of 2.3 g of 10% Pd–C in 300 ml of ethanol at 60° for 10 hr. After filtration of the catalyst, evaporation, and isolation of the basic fraction as described for **27b** the crude, oily base (1.5 g) was dissolved in dry ether and treated with alcoholic HCl. The precipitated hydrochloride was recrystallized from methanol–ether as colorless crystals of **hemihydrate**, mp 237–239°, spectrally devoid of peaks owing to isolated double bonds and not the same as **27b** hydrochloride.

Anal. Calcd for $C_{13}H_{17}N \cdot HCl \cdot 0.5H_2O$: C, 67.08; H, 8.23; N, 6.02. Found: C, 67.10; H, 8.38; N, 6.25.

The same compound was obtained *via* sodium borohydride reduction of **27b**.

2,3,4-Trimethyl-1,4-ethano-1,2,3,4-tetrahydroisoquinoline (31b) Hydroiodide.—Hydrogenation of dioxime **24d** (4.5 g) in ethanol (300 ml) in the presence of 1.5 g of 10% Pd–C was carried out as described under preparation of **29b**, except that shaking was continued for 5 hr until nearly 3 molar equiv of hydrogen had been absorbed. The catalyst was filtered and most of the solvent was evaporated. The oily, basic residue was treated with methyl iodide (10 ml) and warmed for 15 min on a steam cone. Evaporation of excess reagent and addition of a small amount of ether gave 0.8 g of crystals, mp 242–246° dec. Recrystallization from ethanol–ether afforded colorless crystals: mp 258–259° dec; infrared (Nujol) devoid of significant features other than very broad ionic bands at 3.6–3.8 μ; λ_{max}^{EtOH} 247 mμ (ε 290).

Anal. Calcd for $C_{14}H_{19}N \cdot HI$: C, 51.07; H, 6.12; N, 4.25. Found: C, 51.05; H, 6.04; N, 4.21.

Compound 36.—A solution of 5 g of dioxime **24d** in 300 ml of ethanol was hydrogenated in the presence of 5 g of Raney nickel at 60°. A pressure drop of 6 psi took place during the first 1.5 hr. Evaporation of the filtered solution gave basic oil, which was treated with excess iodomethane, whereupon a vigorous exothermic reaction occurred. After 2 hr of reflux with 20 ml of methyl iodide in methanol, the crude material was taken up in water. The aqueous solution was washed with ether and made basic by addition of sodium hydroxide solution. The crude, partly methylated base (3 g) was isolated by extraction with ether, and this oil was then treated again with methyl iodide in refluxing ethanol. The **hydroiodide** was obtained on addition of ether and was recrystallized from ethanol as colorless crystals:

mp 220–221°; λ_{max}^{Nujol} 3.70 μ; λ_{max}^{EtOH} 216, 255 mμ (ϵ 17,160, 120, respectively).

Anal. Calcd for $C_{17}H_{30}I_2N_2$: C, 39.55; H, 5.86; N, 5.43. Found: C, 39.63; H, 5.93; N, 5.46.

Registry No.—**1a**, 2997-20-8; **1c**, 13128-08-0; **2**, 13128-09-1; **3**, 13128-10-4; **4**, 13128-11-5; **5**, 13128-12-6; **6**, 13128-13-7; picrate of **6**, 13128-14-8; **7**, 3293-73-0; **8**, 2997-07-1; 1-mono-2,4-dinitrophenylhydrazone of **8**, 2997-08-2; **10**, 13128-18-2; **12**, 13128-19-3; bis-2,4-dinitrophenylhydrazone of **12**, 13128-20-6; monooxime of **12**, 13128-21-7; **13**, 13128-22-8; **14**, 13221-17-5; oxime of **14**, 13168-37-1; *cis* **15a**, 13128-23-9; *trans* **15a**, 13128-24-0; **15b**, 13128-25-1; **15d**, 13128-26-2; **16a**, 13128-27-3; hydrochloride of **16a**, 13168-38-2; **16b**, 13128-28-4; hydrochloride of **16c**, 13192-30-8; hydrochloride of **17a**, 13128-29-5; hydrochloride of **18a**, 13128-30-8; hydrochloride of **18b**, 13128-31-9; **19**, 13168-39-3; **20**, 13128-32-0; **22**, 13128-33-1; **23**, 13128-34-2; **24a**, 2997-09-3; **24b**, 2997-10-6; **24c**, 2997-40-2; **24d**, 2997-38-8; **25**, 13128-40-0; hydrochloride of **26**, 13128-41-1; **27a**, 3277-16-5; hydrochloride of **27a**, 2997-11-7; picrate of **27a**, 13128-44-4; **27b**, 2959-93-5; hydrochloride of **27b**, 3118-09-0; **28a**, 13128-47-7; hydrochloride of **28a**, 13128-48-8; N-acetyl derivative of **28a**, 13128-49-9; hydrochloride of **28b**, 13128-50-2; **29a** (X = I), 2997-13-9; **29a** (X = I·H_2O), 13128-52-4; **29a** (X = Cl·H_2O), 13128-53-5; **29a** (X = Cl·1.5H_2O), 13128-54-6; **29a** (X = Br), 3196-51-8; **29b** (X = I), 2959-88-8; **30a**, 2997-34-4; **31a**, 13128-58-0; picrate of **31a**, 13128-59-1; hydrochloride of **31a**, 13128-60-4; hydroiodide of **31a**, 13128-61-5; methyl iodide of **31a**, 3048-72-4; hydroiodide of **31b**, 13128-63-7; **32a**, 2997-33-3; **33a**, 13128-65-9; **36**, 13128-66-0; 4,4-diphenyl-1,3-cyclohexanedione, 13128-74-0; $C_{18}H_{16}O_2$ (mp 244–248), 13128-75-1; 2-benzyl-3,4-dimethyl-1,4-dihydro-1,4-ethanoisoquinolinium bromide, 2959-89-9; 2-benzyl-3,4-dimethyl-1,4-dihydro-1,4-ethanoisoquinolinium iodide, 3123-56-6; $C_{20}H_{22}IN$, 2997-14-0; $C_{22}H_{26}IN$, 2997-15-1; $C_{21}H_{24}IN$, 2997-18-4; $C_{25}H_{24}ClN \cdot 0.5H_2O$, 2997-16-2; $C_{26}H_{26}IN$, 2997-17-3; $C_{22}H_{25}BrNO_2$, 2997-19-5; $C_{22}H_{24}ClNO_2 \cdot 0.5H_2O$, 3123-45-3.

Acknowledgments.—We cordially thank the following people for help given during this work: Mr. George Robertson, Mr. Rudolf Oeckinghaus, Mr. James Mitchell, and Mrs. Carol Rodeley for microanalyses; Miss Natalie Cahoon, Mrs. Margaret Mulligan, Miss Diane Bonney, Mr. Charles Navarro, Miss Jan Siragusa, and Miss Ruth Behnke for spectral data; Mr. Louis Dorfman for aid in analytical work and interpretation of nmr spectra; Mr. Ronald T. Smith for assistance in preparation of intermediates; Dr. John Marsh and Mrs. Angela Aretakis for aid in literature searches; Drs. Carl Rehm and J. Papariello for pK_a and other measurements; and Drs. B. Ziegler, W. Yost, and R. Margerison of the development staff who cooperated in improving certain phases of the synthetic work. We wish to thank Dr. Karl Schenker for suggesting that this material be published in advance of his own work, Drs. A. Renzi, W. Barrett, A. J. Plummer and R. Gaunt for pharmacological testing of compounds, Drs. E. Schlittler and G. deStevens for their support of the program, and Dr. Richard L. Hinman of Union Carbide Co., Tarrytown, N. Y., for a profitable discussion of enamine basicities.

Synthesis of Isoquinolines. VI. N-Alkyl-1,2,3,4-tetrahydroisoquinolines[1]

J. M. BOBBITT, D. N. ROY,[2] A. MARCHAND, AND C. W. ALLEN

Department of Chemistry, The University of Connecticut, Storrs, Connecticut

Received November 23, 1966

A reaction scheme has been worked out which allows the synthesis of substituted N-methyl-1,2,3,4-tetrahydroisoquinolines from substituted benzaldehydes in high over-all yields. Using this method, two alkaloids, corypalline and hydrohydrastinine, have been prepared. Secondly, a method has been devised for preparing N-substituted 1,2,3,4-tetrahydroisoquinolines where the alkyl group is varied from methyl to *t*-butyl. The method uses glycidol followed by periodate oxidation to produce carbons 3 and 4 of the isoquinoline.

Recently, we[3] have described an efficient method for converting substituted benzaldehydes to 1,2,3,4-tetrahydroisoquinolines (**1** → **2** → **3** → **6**) (Scheme I). We have now extended the method to the preparation of N-alkyl-1,2,3,4-tetrahydroisoquinolines.

N-Methylation was carried out as a part of the first reduction step. Thus, the appropriate substituted benzaldehyde was combined with aminoacetal and reduced over platinum oxide. The hydrogenation vessel was opened and a slight excess of formaldehyde and some acetic acid were added after which hydrogenation was continued to carry out the N-methylation.[4] The N-benzyl-N-methylaminoacetals (**4**) were then treated with dilute hydrochloric acid and hydrogenated to yield the desired products (**5**). The reaction was tested on three compounds, vanillin (**1a**), isovanillin (**1b**), and piperonal (**1c**). The yields of **5a**, **5b** (corypalline), and **5c** (hydrohydrastinine) were 59, 94, and 67%, respectively, based on the starting aldehydes. Compound **5b** was isolated as a free base while **5a** and **5c** were isolated as hydrochlorides. As in the original synthesis,[3] there must be an oxygen function in the 3 position of the starting aldehyde for effective cyclization; free phenolic groups do not interfere. It is of interest to note that corypalline (**5b**)[5] and hydrohydrastinine (**5c**)[6] have been prepared previously in yields of approximately 0.3 and 10%.[7]

(1) (a) Paper V: J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind.* (London), 2127 (1966). (b) This work was supported in part by Grant CA-3905 from the National Cancer Institute of the National Institutes of Health.

(2) On leave from the Bengal Immunity Research Institute, Calcutta 16, India; recipient of a Fulbright Travel Grant.

(3) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(4) W. S. Emerson, *Org. Reactions*, **4**, 174 (1948).

(5) R. H. F. Manske, *Can. J. Res.*, **15B**, 159 (1937).

(6) P. Fritsch, *Ann.*, **286**, 1 (1895).

(7) It should be noted that these compounds were prepared for structure elucidation studies in which yields are less important.