that the introduction of laser sources, which can be expected soon, will help to alleviate some of the difficulties by shifting the excitation frequency down the spectrum into the red or near-infrared region. It should also help to reduce the minimum sample size.

Most Raman studies of organic compounds have hitherto dealt with simple molecules and we are now trying to apply the technique to natural products and their derivatives. Measurements on mono- and disubstituted steroids indicate that the spectra are entirely different from the infrared spectra; they are more characteristic of the skeletal structure and less affected by functional groups that impart the strong identifying features on the infrared spectra. Measurements on aqueous solutions of methyl furanosides and methyl pyranosides show that the spectra are simpler than the infrared spectra obtained from solid samples, though we have not yet progressed far in interpreting them.

Molecular spectroscopists would have made little progress in the vibrational analysis of small symmetric molecules if they had been dependent on the infrared spectra alone, and one cannot expect to achieve a full interpretation of the vibrational behavior of more complex organic compounds until our understanding of the Raman spectra comes into better balance with our knowledge of the infrared spectra.

Acknowledgment.—We wish to thank Mr. George Ensell for his invaluable aid with the modification of the Raman source unit and the construction and maintenance of the lamps. Our thanks are also due to Mrs. M. A. MacKenzie for making many of the measurements and checking our results. Dr. Walter Mitura has contributed to the studies with aqueous solutions. We also wish to acknowledge the valuable contributions of Dr. P. J. Krueger and Dr. K. Noack who participated in the preliminary phases of this work, and to Dr. H. J. Bernstein with whom we have had many enlightening discussions. It is not inappropriate to add in conclusion that the trials and tribulations we have encountered in the course of these studies have recalled nostalgic memories of Room MB-4 at Mallinckrodt Laboratory at Harvard University. There, during the period 1938–1942, the enthusiasm of Professor Fieser encouraged the senior author to persevere in the then new field of ultraviolet spectrometry, where problems of a similar character were encountered.

2,2,4-Trimethyl-1,2-dihydroquinolines. Preparation and Nuclear Magnetic Resonance Studies*,[1]

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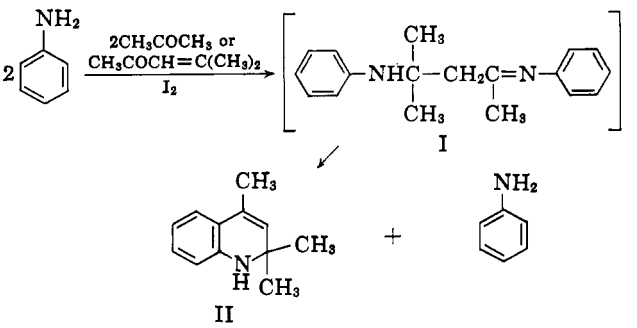
The structures of the "acetone anils" of *m*-toluidine, *m*-chloroaniline, and *m*-anisidine have been established to be 2,2,4,7-tetramethyl-1,2-dihydroquinoline (IVa), 7-chloro-2,2,4-trimethyl-1,2-dihydroquinoline (IVb), and 7-methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (IVc), respectively, on the basis of n.m.r. spectrometric evidence. An analysis of the chemical shifts and splitting patterns of the aromatic protons in these and other related 1,2-dihydroquinoline derivatives has been carried out, with special emphasis on several substituent effects and, in one instance, on the influence of solvent.

2,2,4-Trimethyl-1,2-dihydroquinoline (II) and its analogs, readily prepared by condensation of the appropriate substituted aniline with acetone[2,3] or mesityl oxide[4] in the presence of iodine as a catalyst, were first formulated incorrectly by Knoevenagel[2] in 1921 as "acetone anils," or simple Schiff bases of acetone. The currently accepted structure of these products was first proposed independently on purely chemical grounds by Reddelien and Thurm,[5] by Cliffe,[6] and by Murray and co-workers,[7] and has since been substantiated by a variety of ultraviolet,[8,9] infrared,[10] and n.m.r.[10-13] spectrometric evidence. Following an earlier suggestion of Rosser and Ritter,[14] Tung[11] has recently shown that the formation of II probably proceeds by way of intermediate adduct I, which cyclizes with elimination of a molecule of arylamine. The novel conversion of II·HCl into 2-guanidino-4-methylquinazoline hydrochloride (III·HCl) on treatment with dicyandiamide,



* To Professor Louis F. Fieser.

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

(2) E. Knoevenagel, *Ber.*, **54**, 1722 (1921).

(3) W. R. Vaughan, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 329.

(4) E. Knoevenagel, *Ber.*, **56**, 2414 (1923).

(5) J. Reddelien and A. Thurm, *ibid.*, **65**, 1511 (1932).

(6) W. H. Cliffe, *J. Chem. Soc.*, 1327 (1933).

(7) J. T. Murray, W. F. Short, and R. Stansfield, *J. Am. Chem. Soc.*, **55**, 2805 (1933).

(8) W. S. Johnson and B. G. Buell, *ibid.*, **74**, 4517 (1952).

(9) D. Craig and E. C. Gregg, Jr., *ibid.*, **75**, 2252 (1953).

(10) I. W. Elliott, Jr., and P. Yates, *J. Org. Chem.*, **26**, 1287 (1961).

(11) C. C. Tung, *Tetrahedron*, **19**, 1685 (1963).

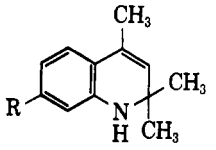
(12) E. J. Zobian, W. S. Kelley, and H. C. Dunathan, *J. Org. Chem.*, **29**, 584 (1964).

(13) J. P. Brown and L. M. Jackman, *J. Chem. Soc.*, 3132 (1964).

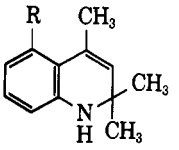
(14) C. M. Rosser and J. J. Ritter, *J. Am. Chem. Soc.*, **59**, 2179 (1937).

which has been described and generalized by Brown,[15,16] has been extended in this laboratory[17,18] to the preparation of various substituted derivatives of III·HCl.

The study of substituted derivatives of 2,2,4-trimethyl-1,2-dihydroquinoline (II) has hitherto been confined principally to those bearing a substituent at C-6. In large measure, this is undoubtedly due to the fact that such derivatives, being obtained from *para*-substituted anilines, can be assigned an unequivocal structure. "Acetone anils" derived from *meta*-substituted anilines, on the other hand, can theoretically have two possible structures, IV or V, since the postulated intermediates corresponding to I can cyclize in either of two directions. In the present investigation, three *meta*-substituted anilines were converted into "acetone anils" by various methods and subjected to n.m.r. spectrometric analysis in an effort to establish their exact structures. Two of these, derived from *m*-toluidine[2,6] and *m*-chloroaniline,[6] respectively, were known prior to this investigation but could not be assigned a definite structure until now. The third, derived from *m*-anisidine, has not been reported previously.

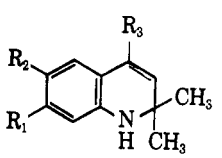


IVa, R = CH_3
b, R = Cl
c, R = CH_3O



Va, R = CH_3
b, R = Cl
c, R = CH_3O

The "acetone anils" of *m*-toluidine, *m*-chloroaniline, and *m*-anisidine have been shown to be the C-7-substituted 2,2,4-trimethyl-1,2-dihydroquinoline derivatives IVa, IVb, and IVc, respectively, on the basis of the n.m.r. spectrometric evidence presented in part in Figures 1–3. A complete tabulation of the n.m.r. data for all "acetone anils" examined in this work is shown in Table I. Spectra for all compounds were obtained in carbon tetrachloride solutions of equal concentration (see Experimental) in order to minimize any possible effects on the chemical shifts that might arise from solvent–solute interaction, particularly in the aromatic proton region.[19] Included also in the study for comparison were the compounds 2,2,4,6-tetramethyl-1,2-dihydroquinoline (*p*-toluidine "acetone anil") (VI), 2,2,4,6,7-pentamethyl-1,2-dihydroquinoline (3,4-xylidine "acetone anil") (VII),[18] and 2,2,6-trimethyl-1,2-dihydroquinoline (VIII).[20,21] The data proved in every case to be in good agreement with the values published previously for "acetone anils" II[10,11] and IX,[11] derived from aniline and *p*-phenetidine, respectively.



VI, R_1 = H; R_2 = R_3 = CH_3
VII, R_1 = R_2 = R_3 = CH_3
VIII, R_1 = R_3 = H; R_2 = CH_3H_2
IX, R_1 = H; R_2 = EtO; R_3 = C

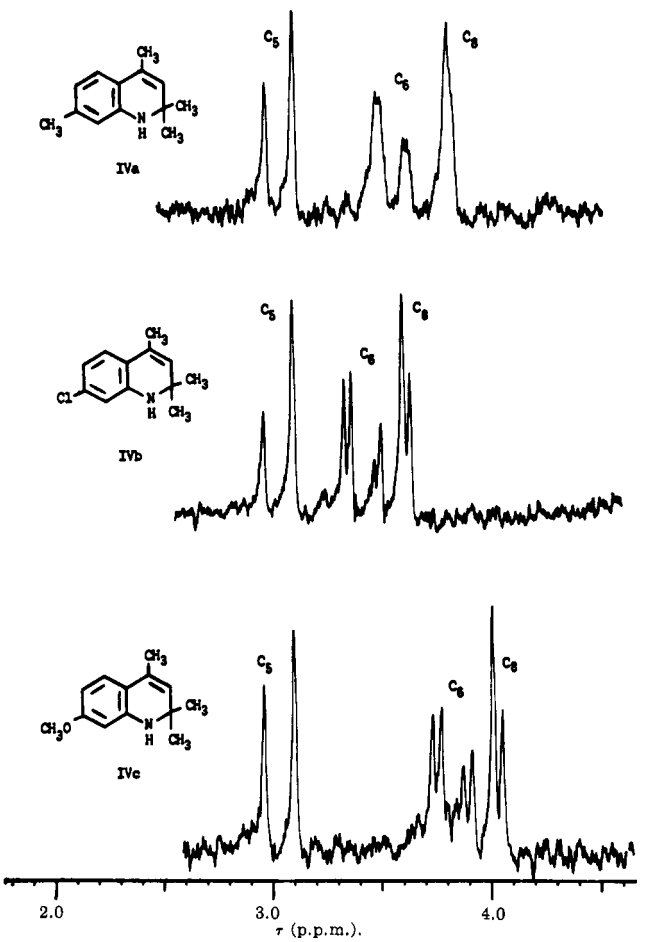


Figure 1.—N.m.r. spectra of C-7-substituted 1,2-dihydroquinolines in carbon tetrachloride. Aromatic proton region.

Although complete spectra were obtained with all the compounds included in this study, particular attention was focused upon the aromatic proton region in order to assign unambiguous structures to the "acetone anils" derived from *meta*-substituted anilines. The data for the aromatic protons of each compound are considered with reference to the following points: (1) the existence or absence of a shielding effect by the nitrogen atom, (2) the shielding or deshielding effect of various aromatic ring substituents, (3) the splitting patterns produced by *ortho* and *meta* coupling between aromatic protons, and (4) the effect of superimposed fine structure arising from interactions between methyl substituents and aromatic protons.

Analysis of the aromatic region of the n.m.r. spectrum of *m*-toluidine "acetone anil" (see Figure 1) reveals a pattern consistent with structure IVa and inconsistent with the alternate form Va. The C-5 proton in IVa, which is situated *meta* to the nitrogen atom and is therefore insulated from its mesomeric effect, is coupled with the C-6 proton and appears as a doublet ($J_o \sim 8$ c.p.s.) at τ 3.05. The C-6 proton, which is shielded as a result of the mesomeric effect of the *para* nitrogen atom, is

(15) J. P. Brown, *Chem. Ind.* (London), 233 (1960); *J. Chem. Soc.*, 3012 (1964).

(16) J. P. Brown, British Patents 900,779 (1962) and 908,187 (1962); *Chem. Abstr.*, **58**, 533, 4583 (1963).

(17) A. Rosowsky, H. Kangur Protopapa, P. J. Burke, and E. J. Modest, *J. Org. Chem.*, **29**, 2881 (1964).

(18) A. Rosowsky, H. Kangur Protopapa, and E. J. Modest, *ibid.*, **30**, 285 (1965).

(19) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 428.

(20) Prepared from a sample of the hydrochloride salt[21] generously donated by Dr. Nelson R. Easton of the Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind.

(21) N. R. Easton and D. R. Cassady, *J. Org. Chem.*, **27**, 4713 (1962).

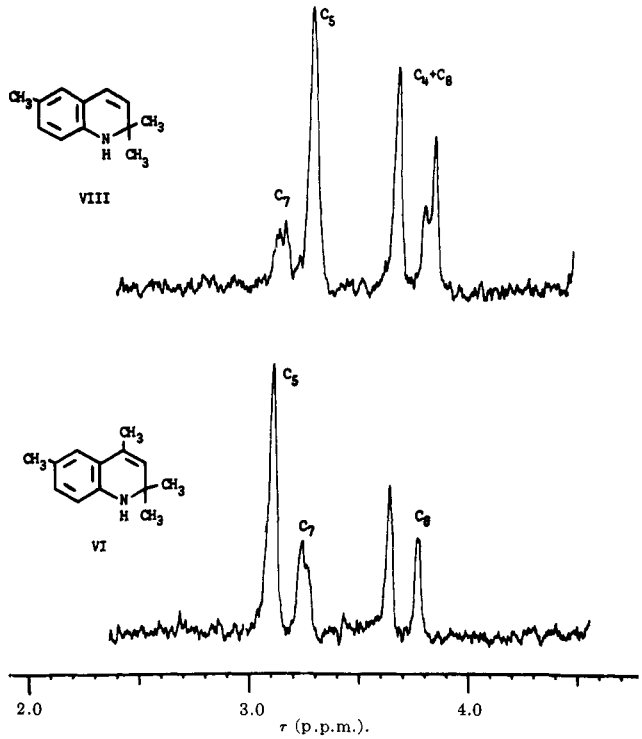


Figure 2.—N.m.r. spectra of C-6-substituted 1,2-dihydroquinolines in carbon tetrachloride. Aromatic proton region.

coupled with the C-5 proton and produces a second doublet ($J_o \sim 8$ c.p.s.) displaced upfield to τ 3.58. The C-8 proton, which is *ortho* to the nitrogen and is likewise shielded by resonance, appears as a single peak shifted still higher to τ 3.83. Additional interaction of the C-8 proton with the protons of the methyl group at C-7 in IVa (*cf.* the C-8 protons in IVb and IVc) is believed to be responsible for the superimposed fine structure in the C-8 proton peak. This interaction apparently obscures the effect of *meta* coupling between the C-6 and C-8 protons, so that only a single peak is observed for the latter,[22] instead of the expected 2–3-c.p.s. splitting.[23] The same argument can be invoked to account for the fact that the C-6 proton appears as only a doublet with poorly defined additional fine structure, rather than as the expected quartet. The significant upfield displacement of the chemical shift of the C-8 proton relative to that of the C-6 proton ($\Delta\tau$ +0.25 in IVa) remains remarkably constant within a series of closely related analogs (see also the values for IVb and IVc in Table I). This difference in the degree of shielding at C-6 and C-8 is consistent with the findings of Corio and Dailey[24] concerning the influence of $-NH_2$ or $-NHCH_3$ substituents on the chemical shifts of *ortho* and *para* protons.

The aromatic proton pattern of the "acetone anil" of *m*-chloroaniline (see Figure 1) indicates this compound to

(22) Similar absence of visible *meta* coupling was observed (in deuteriochloroform solution) for the C-6 proton of 2,5-dimethylaniline, which produced a single peak at τ 3.59. The C-3 and C-4 protons appeared, respectively, as doublets centered at τ 3.04 ($J_o \sim 8$ c.p.s.) and 3.24 ($J_o \sim 8$ c.p.s.). Thus, the over-all aromatic proton pattern of this model compound conformed closely in its essential aspects to that of IVa, IVb, and IVc. A further argument against isomeric structures Va, Vb, and Vc was supplied by the spectrum of 2,3-dimethylaniline. The latter exhibited, among other features, a quartet centered at τ 3.04 ($J_o \sim 8$ and $J_o' \sim 8$ c.p.s.) corresponding to the C-5 proton flanked by two adjacent protons at the *ortho* positions.

(23) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 85.

(24) P. L. Corio and B. P. Dailey, *J. Am. Chem. Soc.*, **78**, 3043 (1956).

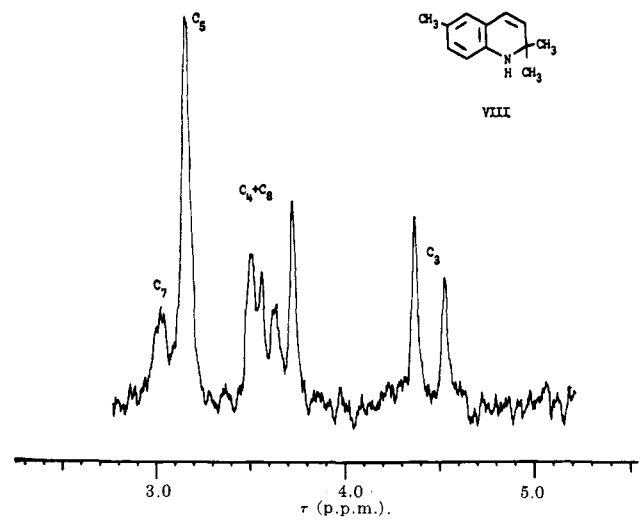


Figure 3.—N.m.r. spectrum of 2,2,6-trimethyl-1,2-dihydroquinoline (VIII) in deuteriochloroform. Aromatic proton region.

be 7-chloro-2,2,4-trimethyl-1,2-dihydroquinoline (IVb), and not the alternate 5-chloro structure Vb. The downfield doublet ($J_o \sim 8$ c.p.s.) at τ 3.03 is assigned to the C-5 proton, which is *meta* to the C-7 chloro substituent and appears to be essentially unaffected by it (*cf.* the C-5 proton of IVa). The C-6 proton produces a well-defined quartet ($J_o \sim 8$ and $J_m \sim 2$ c.p.s.) centered at τ 3.42, and the C-8 proton produces a doublet ($J_m \sim 2$ c.p.s.) at τ 3.66. In this case, *meta* interaction of the C-6 and C-8 protons is clearly visible, in contrast to IVa, in which the corresponding protons appear essentially as only a doublet and single peak, respectively. Small downfield displacements of the C-6 proton ($\Delta\tau$ −0.16) and C-8 proton ($\Delta\tau$ −0.17) are observed in IVb relative to IVa. This finding is consistent with, although somewhat greater than, the substituent effect ($\Delta\tau$ −0.10) noted by Corio and Dailey[24] for chlorobenzene relative to toluene (in cyclohexane solution).

Analogous arguments permit structure IVc to be assigned to the hitherto unreported "acetone anil" of *m*-anisidine. The C-5 proton doublet ($J_o \sim 8$ c.p.s.) at τ 3.03 is not significantly displaced with respect to the C-5 protons of IVa and IVb. This apparent lack of effect on the chemical shift of an aromatic proton by a *meta*-methoxy substituent is noteworthy, in view of the observation by Corio and Dailey[24] of such an effect in simple benzene derivatives. The C-6 proton manifests itself as a well-resolved quartet ($J_o \sim 8$ and $J_m \sim 2$ c.p.s.) centered at τ 3.82, and the C-8 proton as a doublet ($J_o \sim 2$ c.p.s.) at τ 4.05. Once again, *meta* coupling of the C-6 and C-8 protons is evident in the splitting pattern. In contrast to IVb, however, the C-6 and C-8 protons in IVc absorb at a higher field than the corresponding protons in IVa. The magnitude of this upfield displacement ($\Delta\tau$ +0.24 for C-6 and +0.22 for C-8) is in excellent accord with the substituent effect ($\Delta\tau$ +0.23) observed in anisole relative to toluene.[24]

Comparison of the aromatic proton region of VI with that of the isomeric compound IVa shows a consistent pattern strengthening the analysis carried out above for IVa, IVb, and IVc. In contrast to IVa, which contains only one aromatic proton *meta* to the nitrogen atom, VI contains two (at C-5 and C-7). The upfield doublet ($J_o \sim 8$ c.p.s.) at τ 3.70 is thus automatically assigned to the nitrogen-shielded C-8 proton. The re-

TABLE I

N.M.R. SPECTRA OF 1,2-DIHYDROQUINOLINES[a]

Compd.	*gem*-Me_2	Vinyl Me	Aromatic Me	Amine H	Vinyl H	Aromatic protons C-5	C-6	C-7	C-8
IVa	8.81 (6)	8.07 (3)[b]	7.70 (3)	6.65 (1)	4.80 (1)[c]	3.05 (1)[d]	3.58 (1)[e]	...	3.83 (1)[f]
IVb	8.80 (6)	8.08 (3)[b]	...	6.43 (1)	4.72 (1)[c]	3.03 (1)[d]	3.42 (1)[g]	...	3.66 (1)[h]
IVc[i]	8.80 (6)	8.07 (3)[b]	...	6.43 (1)	4.85 (1)[c]	3.03 (1)[d]	3.82 (1)[g]	...	4.05 (1)[h]
VI	8.80 (6)	8.03 (3)[b]	7.76 (3)	6.70 (1)	4.71 (1)[c]	3.10 (1)[f]	...	3.19 (1)[e]	3.70 (1)[d]
VII[j]	8.82 (6)	8.04 (3)[b]	7.88 (6)	6.75 (1)	4.80 (1)[c]	3.18 (1)[f]	...	...	3.83 (1)[f]
VIII[k]	8.80 (6)	...	7.81 (3)	6.61 (1)	4.60 (1)[c]	3.30 (1)[f]	...	3.22 (1)[e]	3.74 (1)[d]
VIII[l]	8.71 (6)	...	7.77 (3)	6.51 (1)	4.45 (1)[m,n]	3.17 (1)[f]	...	3.10 (1)[e]	3.57 (1)[e]

[a] Unless otherwise specified, all spectra were obtained with 2.0 *M* solutions in carbon tetrachloride. Chemical shifts are expressed as τ values in p.p.m. with reference to tetramethylsilane. Estimated relative peak areas shown in parentheses. [b] Doublet ($J \sim 1.5$ c.p.s.). [c] Partly resolved quartet. [d] Doublet ($J_o \sim 8$ c.p.s.). [e] Doublet ($J_o \sim 8$ c.p.s.) with partly resolved fine structure. [f] Single peak. [g] Quartet ($J_o \sim 8$ and $J_m \sim 2$ c.p.s.). [h] Doublet ($J_m \sim 2$ c.p.s.). [i] CH_3O protons, τ 6.30 (3), single peak. [j] See ref. 18. [k] See ref. 20. [l] In deuteriochloroform. [m] Doublet ($J_{cis} \sim 10$ c.p.s.). [n] C-4 vinyl proton: τ 3.77 (1) in CCl_4 and 3.66 (1) in $CDCl_3$, doublet ($J_{cis} \sim 10$ c.p.s.).

maining asymmetric pair of peaks is interpreted as consisting of a doublet ($J_o \sim 8$ c.p.s.) at τ 3.19 and of a single peak at τ 3.10, which exactly overlaps one of the peaks of the doublet and thereby obscures it from view. These features must be ascribed to the C-7 and C-5 protons, respectively. Once again, as in IVa, interference with the manifestation of *meta* coupling is evident, and is presumably attributable to the presence of an intervening methyl substituent at C-6.

The aromatic proton region of VIII was next examined in an effort to assess the possible influence of the C-4 methyl group on the C-5 proton in VI and, by analogy, in other compounds of this series. It is evident from the data in Table I and Figure 2 that, although the C-7 and C-8 protons of both VI and VIII resonate at approximately the same frequency, a distinct downfield displacement ($\Delta\tau$ −0.20) is produced in the C-5 proton peak of VI relative to VIII. This difference suggests that the C-5 proton is deshielded in some fashion by the *peri*-methyl substituent at C-4, both in VI and in other members of the series studied.[25]

In addition, compound VIII unexpectedly provided an interesting illustration of the effect of solvent variation on the aromatic proton pattern (see Table I). In carbon tetrachloride, the downfield asymmetric pair of peaks appears to consist of a singlet at τ 3.30, assigned to the isolated C-5 proton, and of a C-7 proton doublet ($J_o \sim 8$ c.p.s.) centered at τ 3.22. As in the case of VI, the upfield half of this doublet is masked by the overlapping C-5 proton peak, and the visible downfield half is broadened by unresolved fine structure produced by the C-6 methyl substituent. Although a slight displacement of the downfield peaks to lower values ($\Delta\tau$ −0.13 and −0.12 for the C-5 and C-7 protons, respectively) was observed when deuteriochloroform was used in place of carbon tetrachloride, the change did not alter the basic pattern of these peaks. With the remainder of the aromatic proton region, however, a pronounced difference became immediately apparent, as may be seen by comparison of Figures 2 and 3. In carbon tetrachloride (see Figure 2), the C-8 proton doublet centered at τ 3.74 ($J_o \sim 8$ c.p.s.) is only half-visible. Its downfield portion apparently coincides exactly with the downfield half of the C-4 vinyl proton doublet centered at τ 3.77 ($J_{cis} \sim 10$ c.p.s.). In contrast, however, when the spectrum was determined in deuteriochloroform (see Figure 3), the two doublets became clearly revealed. The C-8 aromatic proton doublet and the C-4 vinyl proton doublets are centered in this instance at τ 3.57 ($J_o \sim 8$ c.p.s.) and τ 3.66 ($J_{cis} \sim 10$ c.p.s.), respectively. Replacement of carbon tetrachloride by deuteriochloroform thus appears to produce a greater downfield displacement for the C-8 aromatic proton ($\Delta\tau$ −0.17) than for the C-4 vinyl proton ($\Delta\tau$ −0.11). This differential solvent effect is evidently sufficient to allow visualization of the two protons as a distinct pair of doublets.

In summary, an examination of the aromatic proton region of the n.m.r. spectra of a series of substituted 2,2,4-trimethyl-1,2-dihydroquinolines has been carried out, with special emphasis on the elucidation of substituent effects and, in one case, of a solvent effect. This analysis has made possible the unambiguous formulation of three "acetone anils" derived from *m*-toluidine, *m*-chloroaniline, and *m*-anisidine, respectively, as the C-7-substituted derivatives IVa, IVb, and IVc, rather than the alternative C-5-substituted isomers Va, Vb, and Vc. Additional aspects of the chemistry of these and other "acetone anils" are presently under investigation in this laboratory and will be communicated at a future date.

Experimental[26]

Ultraviolet absorption spectra were measured with a Cary Model 11 spectrophotometer at pH 1 in ethanolic 0.1 *N* hydrochloric acid and at pH 10 in ethanolic 0.05 *M* sodium carbonate–sodium borate buffer. Infrared spectra were determined on liquid films with a Perkin-Elmer Model 137B spectrophotometer. N.m.r. spectra were obtained with 2.0 *M* carbon tetrachloride or deuteriochloroform solutions by means of a Varian A-60 instrument with tetramethylsilane as the internal reference. Thin layer chromatography was carried out on silica gel containing calcium sulfate as a binder, with *n*-butyl alcohol–ammonia–water (100:2:16) as the solvent system. Melting points are corrected and were taken in sealed Pyrex capillaries at 2°/min. in a modified Wagner–Meyer melting point apparatus.[27] Decomposition points may not be precisely reproducible unless conditions are carefully controlled. Except for IVa, procedure B, all per

(25) A similar deshielding effect has been reported [W. Nagata, T. Terasawa, and K. Tori, *J. Am. Chem. Soc.*, **86**, 3746 (1964)] with 2-methoxy-5,6,7,8-tetrahydronaphthalene and 2-methoxy-5-methyl-5,6,7,8-tetrahydronaphthalene, in which the C-4 protons absorb at τ 3.04 and 2.88, respectively. The downfield displacement ($\Delta\tau$ −0.16) of the C-4 proton chemical shift in the latter compound is presumably attributable to the presence of the methyl substituent at C-5.

(26) Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(27) E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938).

cent yields are based on 50% theoretical consumption of starting arylamine and are corrected for arylamine actually recovered.

2,2,4,7-Tetramethyl-1,2-dihydroquinoline (IVa). A.—A solution of *m*-toluidine (290 g., 2.71 moles), acetone (90 ml.), and iodine (5 g.) was refluxed for 60 hr.,[2,6] the internal temperature of the mixture rising gradually to a maximum of 105°. Excess acetone and the water formed in the reaction were removed by distillation at water aspirator pressure, and the dark brown liquid residue was subjected to vacuum distillation. The following fractions were obtained: (1) b.p. 67–83° (0.7 mm.), 179 g. (62% recovery) of unchanged *m*-toluidine; and (2) b.p. 83–103° (0.7 mm.), 62.5 g. (32%), crude IVa. Fraction 2 was redistilled through a 10-in. Vigreux column and the following fractions were collected: (1) b.p. 35–45° (0.3 mm.), 2.3 g. (0.8% recovery), *m*-toluidine; (2) b.p. 45–93° (0.4 mm.), 0.1 g., intermediate fraction; and (3) b.p. 93–98° (0.3–0.4 mm.), 56.4 g. (29%), nearly colorless analytically pure IVa [lit.[2] b.p. 143.5–144.5° (12 mm.)]. The product solidified on standing in the cold, but liquefied at room temperature and darkened rapidly on exposure to air.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.39; H, 9.13; N, 7.48. Found: C, 83.24; H, 9.35; N, 7.54.

B.—In an alternate approach, a solution of *m*-toluidine (62.0 g., 0.579 mole), aniline mesityl oxide anil [b.p. 77.5–80.0° (0.9–1.0 mm.), prepared in 26% yield by the method of Tung][11] (10.0 g., 0.0578 mole), and *p*-toluenesulfonic acid (0.1 g.) was stirred for 4 hr. in a wax bath maintained at 140°. The reaction mixture was subjected to vacuum distillation directly, the following fractions being obtained: (1) b.p. 47–64° (0.3–0.6 mm.), 55 g. (89% recovery), unchanged *m*-toluidine; and (2) b.p. 90–100° (0.4–0.5 mm.), 3.8 g. (35%), crude IVa. Redistillation of the higher boiling fraction through a 3-in. Vigreux column afforded 2.1 g. (19%) of very pale yellow IVa, b.p. 89–94° (0.3–0.4 mm.), identical with the material obtained in the preceding experiment.

The ultraviolet absorption spectrum of IVa showed λ_{max} in mμ (ε) (EtOH/pH 1) 262 (14,810); (EtOH/pH 10) 229 (39,200), 257–267 (3260, plateau), and 325 (3790). The infrared spectrum (liquid film) showed peaks at 2.91 (NH), 6.04 (olefinic C=C), and 6.18 μ (aromatic C=C).

The **hydrochloride salt** IVa·HCl was prepared by passing anhydrous hydrogen chloride gas through a solution of 2.10 g. (0.0112 mole) of IVa free base in 50 ml. of anhydrous ether. The white solid that precipitated was collected, washed with ether, and dried, yield 2.45 g. (97%). A portion of this solid was purified for analysis by dissolving in a minimum of isopropyl alcohol, treating with Darco,[28] diluting fourfold with ether, and cooling. The small colorless prisms were collected, washed with ether, and dried *in vacuo* at 50° over phosphorus pentoxide for 48 hr., m.p. 209.5–212.5° (lit.[6] m.p. 224°).

Anal. Calcd. for $C_{13}H_{17}N\cdot HCl$: C, 69.78; H, 8.09; Cl, 15.87; N, 6.26. Found: C, 69.84; H, 8.03; Cl, 15.83; N, 6.15.

No evidence could be found by thin layer chromatography for the formation of any of the 2,2,4,5-tetramethyl isomer Va.

7-Chloro-2,2,4-trimethyl-1,2-dihydroquinoline (IVb).—A solution of *m*-chloroaniline (300 g., 2.34 moles), acetone (85 ml.), and iodine (5 g.) was refluxed for 30 hr., during which time the temperature of the refluxing vapor rose to 120°. The dark brown reaction mixture was cooled, diluted with 700 ml. of ether, washed with two 100-ml. portions of 5% sodium thiosulfate, rinsed thoroughly with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The dark brown residue was vacuum distilled and all material boiling below 125° (0.6 mm.) was collected and redistilled through a 6-in. Vigreux column. The following fractions were obtained: (1) b.p. 78–85° (2.5–3.5 mm.) and 40–68° (0.25 mm.), 247 g. (82% recovery), unchanged *m*-chloroaniline; (2) b.p. 68–105° (0.25 mm.), 3.0 g. intermediate fraction; and (3) b.p. 105–120° (0.25 mm.), 61.2 g. (71%), yellow IVb [lit.[6] b.p. 165–175° (20 mm.)]. The product solidified on standing in the cold, and darkened rapidly on exposure to air. Redistillation of fraction 3 afforded analytically pure material, b.p. 112–113° (2.2 mm.).

Anal. Calcd. for $C_{12}H_{14}ClN$: C, 69.38; H, 6.78; Cl, 17.05; N, 6.74. Found: C, 69.75; H, 6.77; Cl, 17.15; N, 6.82.

(28) Darco G-60 activated carbon, Atlas Chemical Industries, Inc., Wilmington, Del.

Attempted condensation of *m*-chloroaniline with aniline mesityl oxide anil according to the method of Tung[11] failed to yield IVb, only starting materials and tar being obtained.

The ultraviolet absorption spectrum of IVb showed λ_{max} in mμ (ε) (EtOH/pH 1) 264 (14,420); (EtOH/pH 10) 231 (39,960), 273 (3130), and 330 (3880). The infrared spectrum (liquid film) showed peaks at 2.91 (NH), 6.05 (olefinic C=C), and 6.26 μ (aromatic C=C).

The **hydrochloride salt** IVb·HCl was prepared in 82% crude yield as with IVa·HCl. For analysis IVb·HCl was dissolved in dilute hydrochloric acid and the hot solution was treated with Darco, filtered, and cooled slowly. The fine colorless needles were collected, washed with a few drops of ice–water, and rinsed with acetone. The twice-crystallized sample was dried *in vacuo* at 100° over phosphorus pentoxide for 24 hr., m.p. 189–193° dec. (lit.[6] m.p. 202° dec.).

Anal. Calcd. for $C_{12}H_{14}ClN\cdot HCl$: C, 58.98; H, 6.22; Cl, 29.06; N, 5.73. Found: C, 59.30; H, 6.28; Cl, 28.80; N, 5.85.

No evidence could be found by thin layer chromatography for the formation of any of the 5-chloro isomer Vb.

7-Methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (IVc).—A solution of *m*-anisidine (182 g., 1.48 moles), acetone (50 ml.), and iodine (1.5 g.) was refluxed for 28 hr., during which time the temperature of the reaction gradually rose to a maximum of 108°. The crude mixture was cooled, taken up in 500 ml. of ether, washed twice with 100 ml. of 5% sodium thiosulfate, rinsed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The dark brown residue was vacuum distilled, and the following fractions were obtained: (1) b.p. 74–91.5° (0.3–0.5 mm.), 124 g. (68% recovery), unchanged *m*-anisidine; (2) b.p. 92–130° (0.3–0.4 mm.), 3 g., intermediate fraction; and (3) b.p. 130–137.5° (0.4–0.5 mm.), 38.4 g. (40%), very pale yellow IVc, solidifying gradually at room temperature in the receiver to a pure white, low-melting, waxy solid. Crystallization from petroleum ether (b.p. 30–60°) afforded small colorless needles, m.p. 67–69°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.78; H, 8.46; N, 6.89. Found: C, 77.02; H, 8.58; N, 6.91.

The ultraviolet absorption spectrum of IVc showed λ_{max} in mμ (ε) (EtOH/pH 1) 267 (14,650); (EtOH/pH 10) 229 (34,620), 276 (3340), and 321 (4630). The infrared spectrum (liquid film) showed peaks at 2.91 (NH), 6.00 (olefinic C=C), and 6.18 μ (aromatic C=C).

The **hydrochloride salt** IVc·HCl was prepared in the same way as IVa·HCl. For analysis, a sample of IVc·HCl was dissolved in hot 95% ethanol, and the solution was treated with Darco, filtered, diluted fourfold with ether containing a trace of hydrochloric acid, and cooled. The twice-crystallized pale yellow crystals were dried at 95° *in vacuo* over phosphorus pentoxide for 24 hr., m.p. 200–203° dec.

Anal. Calcd. for $C_{13}H_{17}NO\cdot HCl$: C, 65.12; H, 7.55; Cl, 14.81; N, 5.84. Found: C, 65.16; H, 7.49; Cl, 14.54; N, 5.71.

No evidence could be found by thin layer chromatography for the formation of any of the 5-methoxy isomer Vc.

2,2,4,6-Tetramethyl-1,2-dihydroquinoline (VI).—Acetone (110 g., 1.9 moles) was added dropwise over a 5-hr. period below the surface of a well-stirred mixture of *p*-toluidine (53.5 g., 0.5 mole) and iodine (1.5 g.) heated in a wax bath maintained at 185°.[3] After cooling and dilution with 200 ml. of benzene, the dark brown solution was extracted three times with 50 ml. of 5% sodium thiosulfate and rinsed with water. The benzene solution was then extracted with several 100-ml. portions of 2 *N* hydrochloric acid. Some solid hydrochloride salt precipitated during this process and was collected, washed with benzene, and added to the combined aqueous extracts. The pH was adjusted to approximately 10 with concentrated ammonia, and the oil that separated out was extracted into ether. The ether solution was rinsed to neutrality with water, treated with Darco, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was vacuum distilled through a 3-in. Vigreux column and the following fractions were obtained: (1) b.p. 70–80° (2.3–2.8 mm.), 26.0 g. (48.5% recovery), unchanged *p*-toluidine, solidifying in the receiver; and (2) b.p. 114–118° (2.3 mm.), 18.9 g. (39%), light yellow VI [lit. b.p. 140° (11 mm.),[2] 144–145° (15 mm.)[6]]. The product solidified on standing in the cold and darkened on exposure to air.

The ultraviolet absorption spectrum of VI showed λ_{max} in mμ (ε) (EtOH/pH 1) 260 (11,130); (EtOH/pH 10) 228 (30,290), 270 (3200, inflection), and 333 (2920). The infrared spectrum (liquid

film) showed peaks at 2.93 (NH), 6.04 (olefinic C=C), and 6.20 μ (aromatic C=C).

The **hydrochloride salt** VI·HCl was prepared and purified for analysis in the same way as IVa·HCl. The twice-crystallized small colorless prisms were dried *in vacuo* at 85° for 72 hr. over phosphorus pentoxide in a closed drying pistol (some sublimation of the sample); m.p. 210–211° dec.

Anal. Calcd. for $C_{18}H_{17}N \cdot HCl$: C, 69.78; H, 8.09; Cl, 15.87; N, 6.26. Found: C, 69.77; H, 8.20; Cl, 15.79; N, 6.18.

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2,4-Diaminopyrimidines from Dicyandiamide. III. Reaction with Monocyclic Ketones*[1-4]

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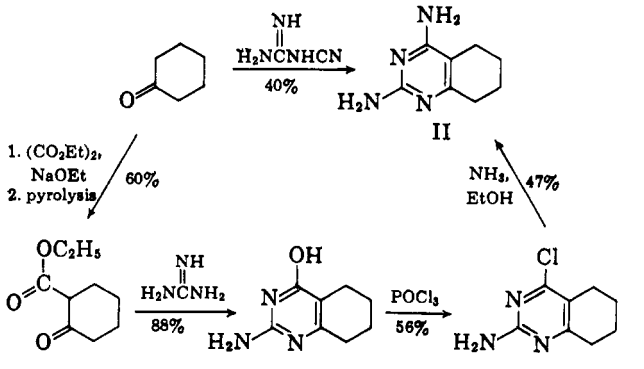
A novel, one-step synthesis of a variety of 2,4-diaminopyrimidine derivatives by condensation of dicyandiamide with monofunctional ketones is reported. The method, which represents a new pyrimidine ring-forming reaction, is general for α-unsubstituted ketones and dicyandiamide or substituted dicyandiamides. This article deals with the preparation of bicyclic 2,4-diaminopyrimido systems from monocyclic ketones. The scope of the reaction is outlined and a reaction mechanism is proposed.

Derivatives of 2,4-diaminopyrimidine are of interest in these laboratories because of the various growth-inhibitory properties, especially antifolic activity, of compounds possessing this biologically versatile ring system.[5-7] In his exhaustive analysis of pyrimidine chemistry, Brown cites three methods of direct synthesis of 2,4-diaminopyrimidines by pyrimidine ring-forming reactions: condensation of guanidine with cyano esters, with malononitriles, and with α-aryl- (or α-alkyl-) β-alkoxyacrylonitriles.[8] The latter route requires the synthesis of an α-cyanocarbonyl compound, alkylation to the enol ether, and condensation with guanidine.[9-11] Another route to 2,4-diaminopyrimidines involves the synthesis of 2-amino-4-hydroxy- or 2,4-dihydroxypyrimidines and subsequent chlorination and amination.[12] Of the foregoing synthetic methods, only the routes from β-alkoxyacrylonitriles and from 4-chloropyrimidines are generally useful for the preparation of 2,4-diaminopyrimidines likely to act as folic acid antagonists, namely, derivatives with carbon substitution at position 5 and, preferably, with carbon or hydrogen substitution at position 6.[6,7] Since each of these two methods is indirect and frequently inefficient, a simpler and more direct route to the requisite 2,4-diaminopyrimidine derivatives would be of obvious importance.

We envisioned a potentially useful, direct route to these compounds in a patent reference[13] in which reaction of dicyandiamide and cyclohexanone was assumed, on the basis of elementary analysis only, to have given 2,4-diamino-5,6,7,8-tetrahydroquinazoline (II). We obtained the same product in 40% yield from dicyandiamide and cyclohexanone and confirmed the structure as 2,4-diamino-5,6,7,8-tetrahydroquinazoline (II) by an independent synthesis.[14] The reaction of guanidine carbonate and 2-carbethoxycyclohexanone gave 2-amino-4-hydroxy-5,6,7,8-tetrahydroquinazoline,[15,16] which was chlorinated to the 4-chloro derivative.[16] Amination of the latter compound afforded the diamine



* To Professor Louis F. Fieser.

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