Structure of the Lower Melting Hydrocarbon Obtained from the Polyphosphoric Acid-catalyzed Condensation of Acetophenone

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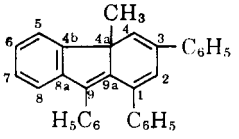
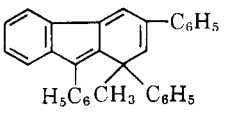
The lower melting hydrocarbon obtained from the polyphosphoric acid-catalyzed condensation of acetophenone is shown to be 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene (I). The assignment of the position of the methyl group is based on the proton magnetic resonance spectra of some phenanthridines which are obtained from the hydrocarbon.

In the presence of polyphosphoric acid, acetophenone has been shown to undergo self-condensation and dehydration.[2] The five products isolated from this reaction were benzoic acid, dypnone, two isomeric hydrocarbons (A and B) of the molecular formula $C_{32}H_{24}$, and a high melting yellow solid (C). The two hydrocarbons, A and B, melted at 181 and 227°, respectively. In an earlier paper of this series[2] two possible structures, I and II, were proposed for the lower melting hydrocarbon, A.



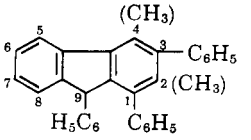
I



II

The nuclear magnetic resonance spectrum of hydrocarbon A exhibits a singlet at $\tau = 8.31$ (with respect to tetramethylsilane, employed as an internal standard), which is in accord with a methyl group attached to an allylic and/or benzylic carbon atom. An AB pattern at $\tau = 3.33$, $\delta\nu = 3$ c.p.s., $J = 1.5$ c.p.s., two thirds of the area of the $\tau = 8.31$ peak, is in accord with two conjugated olefinic hydrogen atoms. The aromatic region is very complex. These data are in accord with either structure I or II. However, with the aid of nuclear magnetic resonance spectroscopy on some of the rearranged products obtained from hydrocarbon A, it is possible to eliminate structure II.

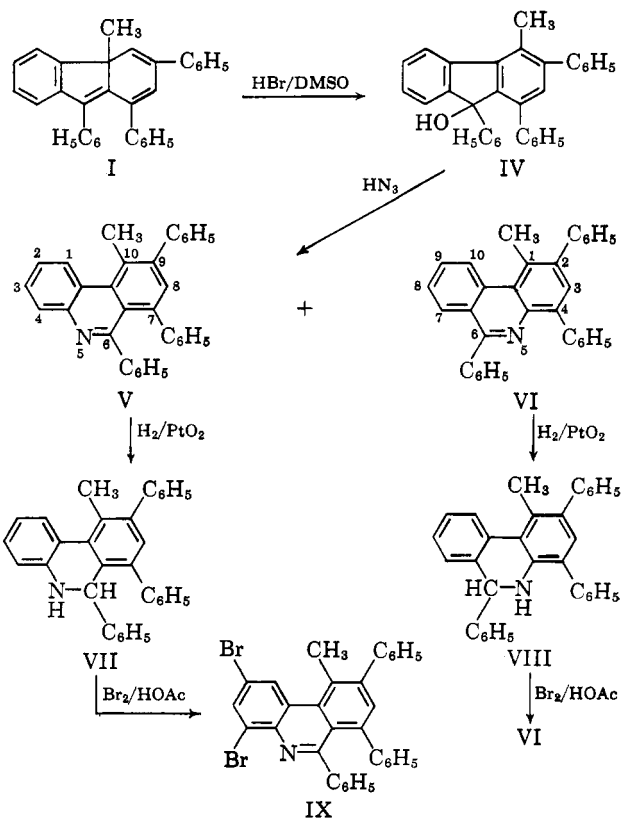
Hydrocarbon A rearranges under the influence of hydrobromic acid in acetic acid to give (2 or 4)methyl-1,3,9-triphenylfluorene (III),[2] most probably by a 1,2-migration of the methyl group. The methyl group of the product should be in the 2-position if II is the structure of hydrocarbon A, or in the 4-position if I is the correct structure.



III

We have found that when hydrocarbon A is treated with 48% hydrobromic acid in dimethyl sulfoxide a good yield of 4-methyl-1,3,9-triphenyl-9-fluorenol (IV) is obtained. Hydrogen bromide in dimethyl sulfoxide is known to act as a brominating agent.[3-6] Fromm[7] has shown that hydrogen bromide and dimethyl sulfoxide react very rapidly to give bromine, water, and dimethyl sulfide. Therefore, it is felt that our reaction proceeds by attack of a positive bromine at position 9 followed by migration of the methyl group and loss of a proton to give 9-bromo-4-methyl-1,3,9-triphenylfluorene. This substance then undergoes hydrolysis to give the observed alcohol, IV. The structure of this alcohol has been established by infrared and nuclear magnetic resonance spectroscopy and by quantitative hydrogenolysis to 4-methyl-1,3,9-triphenylfluorene (III). As will be discussed later, the position of the methyl group in the fluorenol, IV, and, as a consequence, the position of the methyl group in the fluorene, III, have been established by nuclear magnetic resonance spectroscopy.

When 4-methyl-1,3,9-triphenyl-9-fluorenol (IV) was treated with hydrazoic acid, according to the method of



IX

(1) Grateful acknowledgment is made of partial support of this work by a grant from the National Science Foundation (G-6223) and of a Fellowship (1960–1962) to H.W.M. provided by the Phillips Petroleum Co.

(2) R. W. Roeske, D. B. Bright, R. L. Johnson, W. J. DeJarlais, R. W. Bush, and H. R. Snyder, *J. Am. Chem. Soc.*, **82**, 3128 (1960).

(3) H. Gilman and J. Eisch, *ibid.*, **77**, 3862 (1955).

(4) H. Gilman and D. R. Swayampati, *ibid.*, **77**, 5944 (1955).

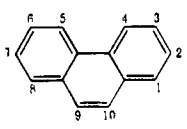
(5) T. L. Fletcher and H.-L. Pan, *J. Org. Chem.*, **24**, 141 (1959).

(6) T. L. Fletcher, M. J. Namkung, and H.-L. Pan, *Chem. Ind.* (London), 660 (1957).

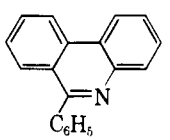
(7) E. Fromm, *Z. Angew. Chem.*, **24**, 1125 (1912).

Arcus,[8] two isomeric phenanthridines (V and VI) were obtained. These two isomeric compounds could be distinguished by reduction of the C=N bond with hydrogen–platinum oxide at 40 p.s.i., giving the two isomeric 5,6-dihydrophenanthridines (VII and VIII). Compound VII contains an aniline residue having unsubstituted *ortho* and *para* positions, while in compound VIII the analogous residue has only a free *meta* position. Therefore, 5,6-dihydro-10-methyl-6,7,9-triphenylphenanthridine (VII) should be susceptible to electrophilic substitution, while its isomer, VIII, should be resistant to such attack. This was found to be true; treatment of compound VII with bromine in acetic acid at room temperature gave the fully aromatic substitution product, 2,4-dibromo-10-methyl-6,7,9-triphenylphenanthridine (IX), but treatment of compound VIII under the same conditions only brought about aromatization, regenerating 1 - methyl - 2,4,6 - triphenylphenanthridine (VI). When the phenanthridines, V and VI, were treated with bromine in acetic acid under the same conditions no reaction took place.

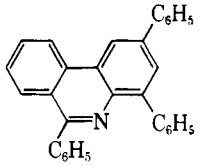
Pople, Schneider, and Bernstein[9] have shown that the protons at the 4- and 5-positions in phenanthrene (X) appear at low field, $\tau = 1.46$, in the nuclear magnetic resonance spectrum. The spectrum consists essentially of two bands with relative intensity 2:8. The assignment of the low-field bands was confirmed by showing that the spectrum of 4-methylphenanthrene consisted of two bands, in the aromatic region, separated by about the same chemical shift as in phenanthrene with intensity ratio of 1:8.[10] The non-equivalence of the protons in phenanthrene is due to the deshielding effect of the magnetic field induced by the ring currents which are set up by the applied magnetic field.[11] Since the protons at the 4- and 5-positions in phenanthrene are in the plane of the ring system and lie closest to the greatest number of rings, they appear at the lowest frequency in the nuclear magnetic resonance spectrum.



X



XI



XII

We have observed this same effect in the phenanthridine series and have used it in assigning the position of the methyl group in the phenanthridines V and VI (see Table I). 6-Phenylphenanthridine (XI)[8] and 2,4,6-triphenylphenanthridine (XII) were synthesized. The former showed low-field absorption at $\tau = 1.47$ and the latter at $\tau = 1.19$. Each of the peaks (at $\tau = 1.47$ and $\tau = 1.19$) observed in spectra of the synthetic phenanthridines (XI and XII) corresponded to two protons. These low-field bands were therefore assigned to the protons at the 1- and 10-positions. The nuclear magnetic resonance spectra of the phenanthridines V and VI showed absorption at $\tau = 1.18$ and 1.14, respectively, each absorption corresponding to a single proton. These low-field protons showed coupling of 8 c.p.s., which is what would be expected for protons at positions 1 and 10 coupled to *ortho* protons.[12] The low-field absorption in the spectrum of compound IX had a coupling constant of 3 c.p.s., which was also expected for coupling of the *meta* protons in the 1- and 3-positions.[12]

TABLE I

PROTON MAGNETIC RESONANCE DATA

Compound	Chemical shift of low protons,[a] τ	Coupling constant J, c.p.s.	Relative intensity	Chemical shift of methyl protons, τ
IV				7.33
V	1.18[b]	8	1	7.04
VI	1.14[b]	8	1	7.05
VII	2.22[b]	8	1	7.44
VIII	2.22[b]	8	1	7.44
IX	1.23[b]	3	1	7.10
X	1.46[c]		2	
XI	1.47[c]		2	
XII	1.19[c]		2	

[a] Protons in the 1- and 10-positions of the phenanthridines and the 4- and 5-positions of phenanthrene. [b] Doublet. [c] Multiplet.

It is also significant that there was a shift of 17.5 c.p.s. to lower field in the methyl group absorption in going from the fluorenol, IV, to the phenanthridines, V and VI. This would be expected if the methyl group was in the 1- or 10-position of the phenanthridines since the methyl protons would be closer to the adjacent benzene ring in the phenanthridines than in the fluorenol. Therefore, the methyl protons would be deshielded by the induced magnetic field of the ring currents and appear at lower field in the nuclear magnetic resonance spectrum.

Additional evidence for the assignment of the position of the methyl group was obtained from the nuclear magnetic resonance spectra of the reduced phenanthridines, VII and VIII. In these compounds the two benzene rings which make up the nucleus of the phenanthridine are no longer coplaner. Now the substituent at the 1- or 10-position is no longer held in the plane of the adjacent benzene ring but can lie above or below that plane and accordingly should show absorption at higher field in the nuclear magnetic resonance spectrum. This shift to higher field was observed. In the dihydrophenanthridines (VII and VIII), the low-field protons showed a shift of 62.4 and 64.8 c.p.s. to higher field as compared to the phenanthridines (V and VI), and the methyl absorption shifted 24 c.p.s. to higher field.

These data allow the unequivocal assignment of the methyl group to the 1-position in compound V and to the 10-position in compound VI. These assignments correspond to the methyl group in the 4-position in the fluorenol, IV, and the fluorene, III, leaving only structure I, 4a-methyl-1,3,9-triphenyl-4a*H*-fluorene, as tenable for hydrocarbon A.

(8) C. L. Arcus and M. M. Combs, *J. Chem. Soc.*, 4319 (1954).

(9) H. J. Bernstein, W. G. Schneider, and J. A. Pople, *Proc. Roy. Soc.* (London), **A236**, 515 (1956).

(10) H. J. Bernstein, W. G. Schneider, and J. A. Pople, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, Inc., New York, N. Y., 1959, p. 250.

(11) H. J. Bernstein, W. G. Schneider, and J. A. Pople, *ibid.*, pp. 181–183.

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

Experimental[13]

Reaction of Acetophenone with Polyphosphoric Acid. Preparation of Hydrocarbon A.[2]—A mixture of 1062 g. of polyphosphoric acid, 492 g. of acetophenone, and 600 ml. of benzene was refluxed with vigorous stirring for 7 hr. The mixture turned green-black and remained that color throughout the reflux period. The green-black polyphosphoric acid layer was separated from the benzene layer while the mixture was still hot; the benzene solution was set aside for recovery of hydrocarbon B (see next paragraph). The acid layer was then poured into 1.5 l. of ice–water. After the ice had melted, the mixture was washed seven times with 250-ml. portions of benzene. Filtration of the aqueous mixture gave about 10 g. of a yellow substance (C), m.p. > 300°. The benzene wash solution was washed twice with 10% sodium hydroxide and once with water. The benzene was removed by distillation under reduced pressure. The yellow solid obtained was washed thoroughly with 500 ml. of low boiling petroleum ether. The yellow crystalline solid was recrystallized twice from a 1:1 mixture of benzene and cyclohexane to give 68 g. of hydrocarbon (A), m.p. 179–181°.

The original benzene layer was washed twice with 10% sodium hydroxide and once with water. The benzene was removed by distillation under reduced pressure. The resulting yellow solid (B) was recrystallized from a 1:1 mixture of benzene and cyclohexane, m.p. 227–229°.

Rearrangement of Hydrocarbon A to 4-Methyl-1,3,9-triphenyl-9-fluorenol.—A solution of 5 g. (0.012 mole) of hydrocarbon A in 150 ml. of dry dimethyl sulfoxide was stirred at 50° and 6.7 g. of 48% hydrobromic acid was added in one portion. The solution immediately turned blue-green. After about 15 min. the color of the solution had changed to yellow. The solution was stirred at 60° for an additional period at 1.25 hr. The yellow solution was then poured into 100 ml. of water. The light yellow solid which formed was dried, dissolved in about 10 ml. of benzene, and chromatographed over neutral alumina. The chromatography was carried out by eluting first with low boiling petroleum ether and then with a 3:1 mixture of methyl alcohol and ether. The alcohol–ether fraction was evaporated under reduced pressure giving 3.5 g. (66.6%) of 4-methyl-1,3,9-triphenyl-9-fluorenol, IV, m.p. 181–183°. Recrystallization four times from a 1:1 mixture of anhydrous ethanol and benzene gave the analytically pure sample, m.p. 182–183°.

Anal. Calcd. for $C_{32}H_{24}O$: C, 90.56; H, 5.66. Found: C, 90.67; H, 5.69.

The infrared spectrum, taken in chloroform, showed a strong resemblance, except for the fingerprint region and the O—H stretching absorption at 3550 cm.$^{-1}$, to the infrared spectrum of 4-methyl-1,3,9-triphenylfluorene, III.[1] The nuclear magnetic resonance spectrum showed methyl absorption (singlet) at τ = 7.33 and the hydroxyl proton appeared at τ = 7.48.

Hydrogenolysis of 4-Methyl-1,3,9-triphenyl-9-fluorenol (IV).—A mixture of 2 g. (0.0048 mole) of 4-methyl-1,3,9-triphenyl-9-fluorenol (IV), 50 ml. of absolute ethanol, and 0.5 g. of Raney nickel (W-2) was shaken in a hydrogenation bomb at 1000 p.s.i. of hydrogen and 100°. Hydrogen uptake was observed for about 5 min. No further uptake was observed over a period of 24 hr. The reaction mixture was then cooled to room temperature and the catalyst was removed by filtration. The solvent was removed by distillation under reduced pressure. The resulting white crystalline solid was recrystallized from absolute ethanol giving 1.9 g. of white needles, m.p. 163–165°. A mixed melting point with 4-methyl-1,3,9-triphenylfluorene[2] (III) showed no depression, m.p. 163–164°.

Reaction of 4-Methyl-1,3,9-triphenyl-9-fluorenol (IV) with Hydrazoic Acid. Preparation of 10-Methyl-6,7,9-triphenylphenanthridine (V) and 1-Methyl-2,4,6-triphenylphenanthridine (VI).—Sodium azide (3.5 g.) was added to chloroform (40 ml.) in a 250-ml., three-necked, round-bottom flask equipped with a Hershberg stirrer and a reflux condenser. The mixture was cooled to 0° by means of an ice–water bath and 12 ml. of concentrated sulfuric acid was added over a period of 30 min. The mixture was stirred for 15 min., and it was then allowed to warm to room temperature. A solution of 7 g. (0.016 mole) of 4-methyl-1,3,9-triphenyl-9-fluorenol (IV) in 70 ml. of chloroform was slowly added over a period of 1.5 hr. Immediately upon addition of the alcohol the mixture became dark yellow-brown. After 1 hr. the stirred solution was light yellow. One hundred and fifty milliliters of water was then added to the reaction mixture and this mixture was stirred for 15 min. The chloroform layer was separated and washed with 100-ml. portions of water, 10% sodium hydroxide, and again with water. The white crystalline solid collected after distillation (under reduced pressure) of the chloroform was washed twice with 100-ml. portions of absolute ethanol (compound V is soluble in ethanol while VI is very insoluble). The remaining solid was recrystallized from a 3:1 mixture of chloroform and absolute ethanol giving 4.9 g. (63%) of 1-methyl-2,4,6-triphenylphenanthridine (VI), m.p. 207–208°.

Anal. Calcd. for $C_{32}H_{23}N$: C, 91.17; H, 5.50; N, 3.32. Found: C, 90.87; H, 5.51; N, 3.27.

Concentration of the alcohol wash solution gave another white solid. Recrystallization from absolute ethanol gave 1.8 g. (25%) of 10-methyl-6,7,9-triphenylphenanthridine (V), m.p. 175–177°.

Anal. Calcd. for $C_{32}H_{23}N$: C, 91.17; H, 5.50; N, 3.32. Found: C, 90.69; H, 5.48; N, 3.39.

Reduction of 10-Methyl-6,7,9-triphenylphenanthridine (V). Preparation of 5,6-Dihydro-10-methyl-6,7,9-triphenylphenanthridine (VII).—A mixture of 1 g. (0.0023 mole) of 10-methyl-6,7,9-triphenylphenanthridine (V), 90 ml. of ethyl acetate and 0.2 g. of platinum oxide in a taped hydrogenation bottle was shaken under hydrogen at 40 p.s.i. for 1 hr. at room temperature. Hydrogen uptake was observed only for about the first 2 min. The catalyst was removed by filtration leaving a beautiful fluorescent lavender-blue solution. The solvent was removed by distillation at reduced pressure leaving a white crystalline solid. Recrystallization from absolute ethanol gave 0.75 g. (78%) of 5,6-dihydro-10-methyl-6,7,9-triphenylphenanthridine (VII), m.p. 173–175°. A 10% chloroform solution of VII showed strong N—H stretching absorption at 3300 cm.$^{-1}$ in the infrared.

Anal. Calcd. for $C_{32}H_{25}N$: C, 90.78; H, 5.91; N, 3.31. Found: C, 90.90; H, 5.98; N, 3.52.

Reduction of 1-Methyl-2,4,6-triphenylphenanthridine (VI). Preparation of 5,6-Dihydro-1-methyl-2,4,6-triphenylphenanthridine (VIII).—A mixture of 2 g. (0.0046 mole) of 1-methyl-2,4,6-triphenylphenanthridine (VI), 140 ml. of ethyl acetate and 0.25 g. of platinum oxide in a taped bottle was shaken under hydrogen at 40 p.s.i. for 1 hr. at room temperature. The catalyst was removed by filtration leaving a beautiful fluorescent lavender-blue solution. The solvent was removed by distillation at reduced pressure giving a white crystalline solid. Recrystallization from a 1:1 mixture of chloroform and absolute ethanol gave 1.5 g. (76%) of 5,6-dihydro-1-methyl-2,4,6-triphenylphenanthridine (VIII), m.p. 148–149°. A 10% solution of VIII in chloroform showed strong N—H stretching absorption at 3350 cm.$^{-1}$ in the infrared.

Anal. Calcd. for $C_{32}H_{25}N$: C, 90.78; H, 5.91; N, 3.31. Found: C, 90.76; H, 6.00; N, 3.43.

Bromination of 5,6-Dihydro-10-methyl-6,7,9-triphenylphenanthridine (VII). Preparation of 2,4-Dibromo-10-methyl-6,7,9-triphenylphenanthridine (IX).—Two tenths of a gram (0.00047 mole) of 5,6-dihydro-10-methyl-6,7,9-triphenylphenanthridine (VII) was dissolved in 25 ml. of glacial acetic acid in a 125-ml. Erlenmeyer flask. Four drops of bromine were added, giving a colored solution. Hydrogen bromide evolved from the reaction mixture. After 15 min. the solution was poured into 100 ml. of water, causing a yellow solid to precipitate. Recrystallization from a 1:1 mixture of chloroform and absolute ethanol gave 0.20 g. (77%) of 2,4-dibromo-10-methyl-6,7,9-triphenylphenanthridine (IX), m.p. 216–218°. A 10% chloroform solution of IX showed no N—H stretching in the infrared. Bromine was detected by sodium fusion and by the Beilstein test.

Anal. Calcd. for $C_{32}H_{21}NBr_2$: C, 66.32; H, 3.62; N, 2.59. Found: C, 66.40; H, 3.70; N, 2.37.

Reaction of 5,6-Dihydro-1-methyl-2,4,6-triphenylphenanthridine (VIII) with Bromine.—Two tenths of a gram (0.00047 mole) of 5,6-dihydro-1-methyl-2,4,6-triphenylphenanthridine (VIII) was dissolved in 80 ml. of glacial acetic acid and four drops of bromine were added. The colored solution was allowed to stand at room temperature for 20 min. and was then poured into 100 ml. of water. The yellow solid which formed was recrystallized from a 1:1 mixture of chloroform and ethanol giving 0.18 g. (90%) of 1-methyl-2,4,6-triphenylphenanthridine (VI), m.p. 205–207°. Mixed melting point with an authentic sample of VI showed no depression. The product obtained from the bromination reaction had an infrared spectrum identical to that of 1-methyl-2,4,6-triphenylphenanthridine (VI).

Attempted Bromination of 1-Methyl-2,4,6-triphenylphenanthridine (VI).—Six tenths of a gram (0.0015 mole) of 2-methyl-

(13) Melting points are uncorrected. Microanalyses were performed by Mr. J. Nemeth and his associates, University of Illinois.

2,4,6-triphenylphenanthridine (VI) was dissolved in 80 ml. of glacial acetic acid and four drops of bromine were added. After the solution was allowed to stand at room temperature for 2 hr., 100 ml. of water was added, causing the precipitation of a yellow solid. This solid was recrystallized from a 1:1 mixture of chloroform and absolute ethanol, giving 0.59 g. of unchanged 1-methyl-2,4,6-triphenylphenanthridine (VI) as shown by mixed melting point and comparison of the infrared spectra.

Attempted Bromination of 10-Methyl-2,4,6-triphenylphenanthridine (V).—A solution of 0.4 g. (0.00094 mole) of 10-methyl-2,4,6-triphenylphenanthridine (V) in 50 ml. of glacial acetic acid was treated with five drops of bromine at room temperature. After 15 min. the solution was poured into 100 ml. of water, causing the precipitation of a yellow solid. Recrystallization from absolute ethanol gave 0.37 g. (91%) of unchanged 1-methyl-2,4,6-triphenylphenanthridine, m.p. 177–179°, identified by mixed melting point and infrared spectrum.

Preparation of 6-Phenylphenanthridine (XI).[8]—One gram of sodium azide was added to 20 ml. of chloroform in a three-necked, round-bottom flask equipped with a Hershberg stirrer, dropping funnel, and condenser. The mixture was kept at 0° while 4 ml. of concentrated sulfuric acid was slowly added (15 min.) and the mixture was allowed to warm to room temperature. A solution of 2 g. (0.0061 mole) of 9-phenyl-9-fluorenol[8] in 10 ml. of chloroform was added over a period of 1 hr. The solution was stirred at room temperature for 1.5 hr. and then poured into 200 ml. of water. The chloroform layer was separated and washed twice with 50-ml. portions of 50% sulfuric acid. The combined aqueous layer was treated with 10% sodium hydroxide, and 1.5 g. (76%) of 6-phenylphenanthridine was collected by filtration, m.p. 105–107°, lit.,[8] m.p. 101–102°.

Preparation of 2,4,6-Triphenylphenanthridine (XII).—One gram of sodium azide was added to 10 ml. of chloroform in a 250-ml. three-necked, round-bottom flask equipped with a reflux condenser, dropping funnel, and a Hershberg stirrer. The mixture was cooled to 0° and 4 ml. of concentrated sulfuric acid was added over a period of 15 min. The mixture was warmed to room temperature and a solution of 2 g. (0.0048 mole) of 1,3,9-triphenyl-9-fluorenol[14] in 40 ml. of chloroform was added over a period of 1 hr. The mixture was stirred at room temperature for an additional hour. One hundred milliliters of water was then added and this mixture was stirred for 15 min. The chloroform layer was separated and washed with 50-ml. portions of water, 10% sodium hydroxide, and again with water. Concentration of the chloroform solution gave a brown oil which on treatment with 200 ml. of absolute ethanol gave a light yellow solid. Recrystallization from a 1:1 mixture of chloroform and absolute ethanol gave 1.2 g. (60%) of 2,4,6-triphenylphenanthridine (XII), m.p. 214–216°. The infrared spectrum in chloroform of XII was very similar to that of 1-methyl-2,4,6-triphenylphenanthridine (VI) and quite different from the spectrum of 10-methyl-6,7,9-triphenylphenanthridine (V).

Anal. Calcd. for $C_{31}H_{21}N$: C, 91.40; H, 5.16; N, 3.44. Found: C, 91.41; H, 5.46; N, 3.53.

Nuclear Magnetic Resonance Spectra.—The nuclear magnetic spectra were recorded by Mr. O. Norton and Mr. D. Johnson with a Varian Associates high resolution spectrometer (Model A-60) working at a frequency of 60 Mc. per sec. Spectra were obtained in deuteriochloroform using tetramethylsilane as an internal standard. Chemical shifts are expressed as shielding values in parts per million as defined by G. V. D. Tiers.[15]

(14) E. P. Kohler and L. W. Blanchard, *J. Am. Chem. Soc.*, **57**, 367 (1935).

(15) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1959).

Tetracyclic Phenothiazines and Related Compounds. IV. Ketoamides Alkylated and Aminoalkylated on Oxygen, and Alkylated and Aminated on Carbon[1]

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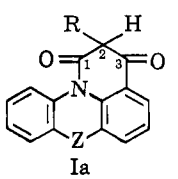
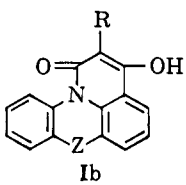
Condensation products of phenothiazine, phenoxazine, carbazole, diphenylamine, and methylaniline with diethyl alkylmalonates (*e.g.*, I and V) form ambident anions with bases. Sodio derivatives of these were alkylated with alkyl halides to give a mixture of C-alkylated and O-alkylated product (Table I), increasing in proportion of the latter as the bulkiness of the halide increased. Known O-methylation products were prepared by use of diazomethane. Some C-amino and C-aminoalkylamino derivatives of these ring systems were prepared by bromination and reaction of the bromo compounds with amines (Table II).

The condensation products of monosubstituted dialkyl malonates with aromatic amines such as methylaniline, phenothiazine, phenoxazine, etc. (*e.g.*, I) possess an "active methinyl" group flanked by two carbonyl (or enolic hydroxyl) groups.[3] They, therefore, have the possibility of being alkylated as ambident anions[4] on either the methinyl carbon or on one of the flanking carbonyl groups in its enolic form (*e.g.*, II).

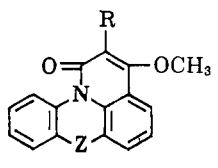
We wished to prepare compounds preferably bearing aminoalkyl groups in each of these positions, in the hope that the combination of "pharmacologically active" side chains of different lengths and polarities with heterocyclic rings of differing sizes and shapes



Ia



Ib



IIa. R = CH_3; Z = S
b. R = C_2H_5; Z = S
c. R = C_2H_5; Z = —

would lead to differing, hopefully useful, types of biological activity. We were also interested in studying the ratio of C- to O-alkylation in this series of compounds to determine whether direct alkylation might replace the bromination followed by amination sequence reported earlier to give compounds fully substituted on carbon 2 of I, and so convertible to aldehydes and ketones.[1]

It was obviously necessary to find a method of telling C-alkylation products from O-alkylation products. Presumably the well known acid-catalyzed decomposition of enol ethers could serve as such a method but

(1) Previous paper: M. Harfenist, *J. Org. Chem.*, **27**, 4326 (1962).

(2) Present address: U. S. Vitamin and Pharmaceutical Corp., Yonkers, N. Y.

(3) Since the numbering system, which is as shown for derivatives of phenothiazine and phenoxazine, differs for the carbazole and the alkylaniline derivatives, we shall name the products I as if they are formed from condensation of the appropriate malonic acid and aromatic amine with loss of water, *e.g.*, I, where R = ethyl and Z = sulfur, will be given the trivial name "ethylmalonylphenothiazine" (see ref. 1). The systematic names for other new compounds are given in the Experimental section.

(4) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269, esp. 6275 (1955).