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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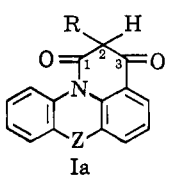
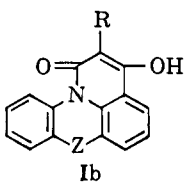
Condensation products of phenothiazine, phenoxazine, carbazole, diphenylamine, and methylaniline with diethyl alkylmalonates (*e.g.*, I and V) form ambident anions with bases. Sodio derivatives of these were alkylated with alkyl halides to give a mixture of C-alkylated and O-alkylated product (Table 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).

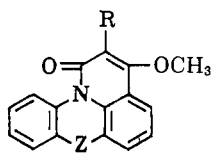
We wished to prepare compounds preferably bearing aminoalkyl groups in each of these positions, in the hope that the combination of "pharmacologically active" side chains of different lengths and polarities with heterocyclic rings of differing sizes and shapes



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).

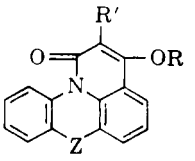
(2) Present address: U. S. Vitamin and Pharmaceutical Corp., Yonkers, N. Y.

(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).

TABLE I

PREPARATION AND PROPERTIES OF OXYGEN-ALKYLATED KETOAMIDES



Z	R′	R	Method of preparation[a]	Yield,[b] %	M.p., °C.	Recryst.[c] solvent	Formula	Analytical—Calcd. C	Calcd. H	Found C	Found H
HH	H	$(CH_2)_3N(CH_3)_2$	C[d]	13	102–103.5	H	$C_{20}H_{22}N_2O_2$	74.51	6.88	74.50	6.98
—	C_2H_5	$(CH_2)_3N$⟨⟩$N-CH_3$	C	32	92–94	H	$C_{25}H_{29}N_3O_2$	74.41	7.24	74.44	7.06
S	CH_3	$(CH_2)_2N(CH_3)_2$	A	23	229[e]	A-EA-A	$C_{20}H_{21}ClN_2O_2S$	61.82	5.44	61.55	5.36
S	C_2H_5	$(CH_2)_2N(CH_3)_2$	A	25	216–220.5[e]	A-E	$C_{21}H_{23}ClN_2O_2S$	62.68	5.76	62.34	5.65
S	C_2H_5	$(CH_2)_3N(CH_3)_2$	B	44	179–186[e]	A-E	$C_{22}H_{25}ClN_2O_2S$	63.43	6.05	63.30	6.16
S	C_2H_5	$(CH_2)_3N$⟨⟩$N-CH_3$	C	47	228–233[f]	M-A-Ac-E	$C_{25}H_{31}Cl_2N_3O_2S$	59.04	6.14	59.39	6.43

[a] The methods of preparation are illustrated in the Experimental section. [b] Yields are reported uncorrected for recovered starting material. [c] Solvents: A = absolute ethanol; Ac = acetone; E = absolute ether; EA = ethyl acetate; H = hexane; M = methanol. [d] Used two moles of sodium ethoxide per mole of "malonyldiphenylamine." [e] Monohydrochloride. [f] Dihydrochloride.

the specific conditions necessary would be best found using a known enol ether.

It was found that the methyl enol ethers of "methylmalonylphenothiazine" (IIa), "ethylmalonylphenothiazine" (IIb), and "ethylmalonylcarbazole" (IIc) could be prepared, the former in poor yield and the latter two in better yield presumably as a result of their higher solubility, when these compounds in ether containing about 10% of methanol were treated with excess of diazomethane for a prolonged period. The catalytic effect of methanol on methylations with diazomethane is a well known phenomenon and, indeed, reaction was imperceptible in the absence of the methanol. Experiments with these known enol ethers revealed that 50% by volume of methanol with the remainder of the solvent either 6 *N* or concentrated hydrochloric acid gave a rapid reversion of enol ether to the acidic "ethylmalonyl-heterocycle" at reflux temperatures. A heating time of at least four hours was therefore regularly used to destroy O-alkylation product II when C-alkylation product III was sought. Some side reaction of "C-ethyl-C-propargylmalonylphenothiazine" (III, R is C_2H_5 and R′ is $CH_2C{\equiv}CH$) appeared to occur under these conditions, perhaps due to addition to the triple bond or partial transformation to an allene, and some decomposition of "C-(2-cyanoethyl) ethylmalonylphenothiazine" (III, R is C_2H_5 and R′ is CH_2CH_2CN) occurred, as anticipated, even after two hours under reflux with the methanolic acid. However the other C-substitution products which were made seemed to be stable.

A single attempt to displace the methoxy group of the methyl enol ether IIb of "ethylmalonylphenothiazine" by several hours of heating under reflux of its solution in piperidine was unsuccessful.

It would be anticipated that O-alkylation of our ambident anions would be favored by increasing the size of the alkylating group, since attack on the oxygen is less subject to steric hindrance than attack on the carbon would be. Our results, all of alkylations done in ethanol or in *t*-butyl alcohol, under essentially similar conditions indicate that C-alkylation of "ethylmalonylphenothiazine" (I, R = C_2H_5, Z = S) occurs to about the same extent as O-alkylation in the cases of methylation (by methyl iodide) and propargylation (by propargyl bromide), while 3-chloropropyl bromide gave only about 20% of C-alkylation. The O-aminoalkyl compounds listed in Table I were prepared essentially free of C-alkylation product, although it should be emphasized that in these cases the mother liquors were not examined for small amounts of C-alkylation products, which presumably were present. Incidentally, it was found that ethylation (with ethyl iodide) of "methylmalonylphenothiazine" and subsequent acid-catalyzed destruction of enol ether led to the same C-alkylation compound as was obtained by methylation (with methyl iodide) of "ethylmalonylphenothiazine." This, of course, serves as an additional proof of structure for both starting materials, and proves the structure of the product.

Cyanoethylation of "ethylmalonylphenothiazine" with acrylonitrile in dioxane–acrylonitrile solution (absence of dioxane led to a marked drop in yield) gave what was apparently only C-alkylation product, since treatment of this product with methanolic acid led to essentially no recovery of "ethylmalonylphenothiazine." However, much unchanged "ethylmalonylphenothiazine" was recovered from the crude reaction mixture by extraction with alkali. Since rapid base-catalyzed reversion of O-cyanoethylated product is a possibility, we are unable to say that O-cyanoethylation did not occur under our conditions.

We have not investigated the effect of changes in solvent on the C-alkylation: O-alkylation ratio. Much recent work in the literature has involved alkylation of phenols, which have been used as simple model substrates.[5] It is not yet clear how many of the conclusions of this work can be carried over unchanged

(5) Results of studies of C-alkylations *vs.* O-alkylation of phenols by allylic and benzyl halides have shown in various cases: (a) increased C-alkylation in solvents with greater hydrogen bonding ability, attributed to a lowered electron availability on the hydrogen bonded enolate oxygen [N. Kornblum, P. J. Berrigan, and W. J. Le Noble, *J. Am. Chem. Soc.*, **82**, 1257 (1960)]; (b) increased O-alkylation in hydroxylic solvents, attributed to increased SN1-like character of the halide in such solvents (ref. 4); (c) an over-riding influence of heterogeneity (which leads entirely to C-alkylation) or homogeneity (leading entirely to O-alkylation) on the product ratio [N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959)].

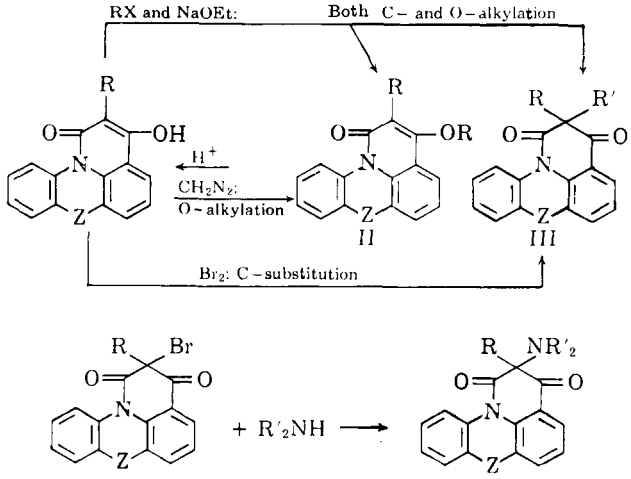
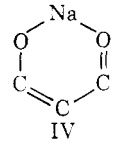


Fig. 1.—Carbon *vs.* oxygen substitution by various routes.

even to alkylations of acyclic diketones. Extension of these ideas to the alkylations of the compounds I would be still more speculative. Indeed, it should be pointed out that conclusions based on alkylation ratios even of dicarbonyl compounds (therefore formally similar to compounds I) which can exist as *cis* (and hence chelate) enols cannot necessarily be carried over to the cases reported here, since the "malonyl compounds" such as I must exist as *trans*, and so necessarily as nonchelate enols. For example, structures proposed[6] by Brändström, to explain C-alkylation of β-diketo compounds, involving metal chelates of the enols (IV), cannot exist in compounds such as I in which both carbonyl groups are part of the same 6-membered ring, for steric reasons. The same caution is undoubtedly necessary, in comparisons involving at least β-diketo compounds with both carbonyl groups in a five- or seven-membered ring.

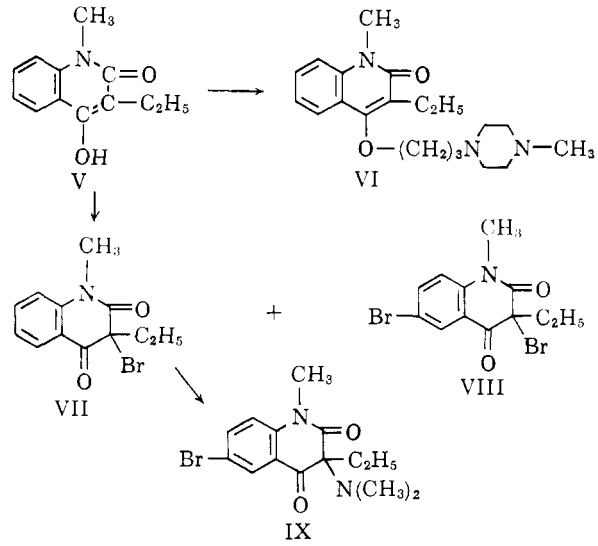


IV

Certainly the influence of heterogeneity[5] can be discounted in the alkylations discussed here, since the sodio enolates of the compounds I are generally extremely soluble in ethanol.

Since substantial amounts of C-aminoalkyl compounds were obviously not going to be available by alkylation of the anion, it was thought that a "pharmacological equivalent" with nitrogen replacing one carbon of a chain might be prepared by use of a bifunctional amine reacting with a C-halo-alkyl malonyl compound. The amines (III, R′ being an amino group) in Table II were made in this way. Although 2-chloroethylmalonylphenothiazine (III, R = C_2H_5 and R′ = Cl) could be readily prepared by direct chlorination of "ethylmalonylphenothiazine," the chlorine proved refractory to displacement by amines under mild conditions. However, the bromo compounds (III, R′ = Br) were readily prepared[1] and reacted reasonably rapidly at room temperature, although yields of purified products were generally not outstandingly good. Some "alkylmalonylarylamine" I was generally recovered from these reactions of bromo compound and amine.

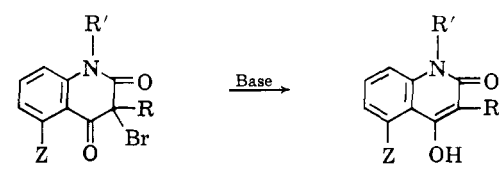
A simpler starting material, "ethylmalonylmethylaniline" V, was subjected to aminoalkylation to give the compound VI, and to bromination to give a mixture of monobromination product VII and a dibromination product presumed to be VIII, each of which contained one bromine readily displaceable by dimethylamine.



V VI VII VIII IX

The preparative details and method of separation are given in the Experimental section. It is of interest that, although more than the theoretical amount of bromine was used, so that free bromine remained at the end of the reaction (as was shown by its co-distillation with the solvent during the work-up), acidic material was recovered from a sodium carbonate wash of the reaction products. It appears that compounds VII and/or VIII can exchange the bromine between the carbonyl groups for hydrogen, presumably by the nuclear bromination of VII to form VIII.

A related bromo compound 3-(3-methylbutyl)-3-bromo-8-methoxy-2,4-[1*H*,3*H*]quinolinedione [*i.e.*, "3-bromo(3-methylbutyl)malonyl-*o*-anisidine"[3]] Xa, has been reported[7] to undergo debromination to XI in high yield when treated with methanolic potassium hydroxide, and in moderate yield when heated with collidine. An analog with the nitrogen methylated, "3-bromobenzylmalonylmethylaniline" Xb underwent appreciable loss of bromine and reversion to "benzylmalonylmethylaniline" when heated with methanolic potassium hydroxide, but no mention of bromination of the benzene ring was made, so presumably the reaction with the methanolic alkali was more rapid than the possible bromination of the benzene ring.



Xa. R = $(CH_2)_2CH(CH_3)_2$, R′ = H, Z = OCH_3
b. R = $CH_2C_6H_5$, R′ = CH_3, Z = H

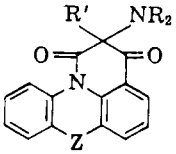
XI

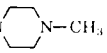
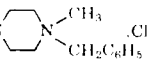
(6) A. Brändström, *Acta Chem. Scand.*, **7**, 223 (1953); from *Chem. Abstr.*, **48**, 3910 (1954).

(7) J. W. Huffman, *J. Org. Chem.*, **26**, 1470 (1961).

TABLE II

CARBON-SUBSTITUTED TETRACYCLIC KETOAMIDES



Z	R′	NR₂	Solvent[a]	Time[b] (days)	Yield,[c] %	M.p., °C.	Recryst. solvent	Formula	Analytical—Calcd. C	Calcd. H	Found C	Found H
O	CH_3	$N(CH_3)_2$	Am	20	34	194–196[d]	A-E	$C_{18}H_{17}ClN_2O_3$[e]	62.80	4.97	63.00	5.04
O	C_2H_5	Br	C	1	51[f]	128–129	A	$C_{17}H_{12}BrNO_3$	57.00	3.36	56.91	3.39
O	C_2H_5	$N(CH_3)_2$	Am	1/12	100	204–206[d,g]	A	$C_{19}H_{18}ClN_2O_3$	Cl^- 9.88		Cl^- 9.71	
O	C_2H_5	$N(CH_3)$—$(CH_2)_3N(CH_3)_2$	Am	24	33	204–212[d] dec.	A-E	$C_{23}H_{29}Cl_2N_3O_3$[h]	57.00	6.43	56.28	6.63
O	C_2H_5		Am	18	39	224–226[d]	A-E	$C_{22}H_{25}Cl_2N_3O_3 \cdot H_2O$[i]	56.75	5.81	56.31	5.71
S	C_2H_5		Ac	5	95	162–170[d,j] dec.	A-Ac-E	$C_{29}H_{30}ClN_3O_2S$	66.99	5.80	66.32	5.77
S	CH_3	$N(CH_3)_2$	B-E	2	38	188–193.5[d]	A-B-E	$C_{18}H_{17}ClN_2O_2S$	60.00	4.75	59.88	5.12
S	CH_3	$N(CH_3)(CH_2)_3N(CH_3)_2$	E	3	31[k]	175–176[d]	A-Ac-E	$C_{22}H_{27}Cl_2N_3O_2S$	56.45	5.82	56.37	6.01
S	C_2H_5		E	5	41	160–162[l]	A-W	$C_{21}H_{20}N_2O_2S$	69.27	5.54	69.16	5.72
S	C_2H_5		E	5	22	172–178.5	Ac-W	$C_{22}H_{22}N_2O_2S$	69.85	5.86	70.27	6.12
S	C_2H_5		E	4	53[m]	146–151[n]	Ac	$C_{22}H_{23}N_3O_2S$	67.41	5.89	67.41	5.85
S	C_2H_5	$N(CH_3)(CH_2)_3N(CH_3)_2$	I-E	4	28[o]	147–155[d]	A-E	$C_{23}H_{29}Cl_2N_3O_2S$	57.25	6.06	57.46	6.67

[a] Solvents: A = commercial absolute ethanol; Ac = acetone; Am = the amine in excess; B = benzene; C = carbon tetrachloride; E = commercial absolute ether; I = isopropyl alcohol; W = water. [b] Reaction at about 30°. Times used were arbitrary, and quite likely are not optimal. [c] Yields are not corrected for recovered starting material. [d] Hydrochloride or dihydrochloride as indicated in formula given. [e] Chloride calcd.: 10.28%. Cl^- found (using silver nitrate with phenosafranine as adsorption indicator): 10.00%. [f] A 46% yield of recovered acidic material was also obtained. This bromo compound was precursor to the three which follow. [g] The crude base had m.p. 90–95°. [h] Cl^- calcd.: 14.23. Cl^- found (phenosafranin): 14.20. [i] Cl^- calcd.: 15.14. Cl^- found (phenosafranine): 14.90. [j] Bubbles make the precise m.p. difficult to determine. [k] Starting material was *impure* bromo compound. [l] Hydrochloride m.p. 214–216° (from A-E). [m] Recovered 27% of the acidic "ethylmalonylphenothiazine." [n] The hydrochloride recrystallized from dilute aqueous hydrochloric acid had m.p. 261–263°. *Anal.* Calcd. for $C_{22}H_{24}ClN_3O_2S$: Cl^- 8.26. Found (phenosafranine method): Cl^- 8.59. [o] Recovered 14% of "ethylmalonylphenothiazine."

Experimental

"2-Chloroethylmalonylphenothiazine" (Compound III: R = C_2H_5; R′ = Cl; Z = S).—Ten grams of finely divided "ethylmalonylphenothiazine" (I, R = C_2H_5; Z = S)[3] was partly dissolved in 750 ml. of carbon tetrachloride under reflux, and cooled to 40°. It was stirred at this temperature and treated with the chlorine generated from 2.4 g. of potassium permanganate by addition of 19 ml. of hydrochloric acid, followed by heating the solution to the boiling point (*ca.* 0.037 mole of chlorine). The resulting solution was washed with water, and then with aqueous sodium carbonate, and dried. Removal of the solvent by distillation at the water pump left 10.1 g. of an orange oil, which crystallized slowly to give m.p. 105–112°. Recrystallization from ethanol and from isopropyl alcohol yielded orange crystals which softened and probably melted at 115–117°, but resolidified and then melted at 155–158°.

Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 62.00; H, 3.67. Found: C, 61.40; H, 3.29.

1-Keto-2-ethyl-3-methoxy-1H-pyrido[3,2,1-*kl*]phenothiazine (Compound IIb).—Diazomethane made from 30 g. (0.14 mole) of N-methyl-N-nitroso-*p*-toluenesulfonamide[8] was dissolved in about 200 ml. of anhydrous ether and was added with stirring to 16.3 (0.055 mole) of "ethylmalonylphenothiazine" partly dissolved in 100 ml. of reagent grade methanol and 1600 ml. of reagent grade anhydrous ether, maintaining the temperature of the solution at 5° during the addition and for 3 hr. more. The solution became homogeneous after 0.5 hr. It was stirred without cooling overnight, and the ether carefully distilled. (The first portions of the distillate contained diazomethane.) The residue after removal of solvent was dissolved in ether and extracted with 1 *N* aqueous sodium hydroxide to remove starting material. (Acidification of the alkaline aqueous layer resulted in a little precipitate.) The ethereal layer was dried and distilled, giving 14.3 g. of b.p. 205–212° at a pressure nominally 0.04 mm. This became crystalline when triturated with ether, and had m.p. 87–103°. Recrystallization from ether and from ethanol gave 8.66 g. of pale yellow crystals, m.p. 110–113°.

Anal. Calcd. for $C_{18}H_{15}NO_2S$: C, 69.82; H, 4.68. Found: C, 69.80; H, 4.66.

4-Methoxy-5-ethyl-6-keto-5,6-dihydro-4H-pyrido[3,2,1-*jk*]carbazole (Compound IIc).—Diazomethane, prepared from 20 g. of N-nitroso-N-methylurea by the "short method"[9] (anticipated yield, 5.6 g., *i.e.*, 0.133 mole of diazomethane) and dissolved in 200 ml. of ether, was dried over potassium hydroxide pellets and added to a stirred suspension of 26.3 g. (0.1 mole) of "ethylmalonylcarbazole"[3,10] in 2 l. of ether and 200 ml. of methanol, with cooling by an ice bath.

After 2 hr., the ice bath was removed and the reaction was stirred for 2 days at 20°. It was then filtered to remove unchanged starting material, and the filtrate was evaporated to dryness to remove diazomethane. The residue was taken up in ether and benzene, and extracted with 250-ml. portions of 4% sodium hydroxide solution. When the dried organic layer was taken down to dryness *in vacuo*, 19.5 g. of a brown oil remained, which slowly solidified, and then had m.p. 74–80°. This was recrystallized three times from hexane for analysis, and had constant m.p. 84–85°.

(8) Method of T. J. de Boer and H. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954). The requisite sulfonamide was purchased from The Aldrich Chemical Co.

(9) F. Arndt, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(10) P. Baumgarten and M. Riedel, *Ber.*, **75B**, 984 (1942).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45. Found: C, 77.95; H, 4.95.

A total of 7.0 g. of starting material was obtained from the initial filtration, and acidification of the sodium hydroxide extracts.

1-Keto-2-methyl-3-methoxy-2,3-dihydro-1H-pyrido[3,2,1-*kl*]-phenothiazine (Compound IIa).—Methylation of "methylmalonylphenothiazine"[1,3] was carried out by stirring 28.1 g. (0.1 mole) of that compound, suspended in a mixture of 250 ml. each of methanol and absolute ether, with the diazomethane generated from 20 g. of nitrosomethylurea[9] for 4 hr. at ice bath temperature and then for 2 days at room temperature. After this time, the bulk of the solid (19.1 g., dry weight) was still not dissolved in the reaction mixture, but was soluble in aqueous sodium hydroxide, hence was unchanged starting material. The alkali-insoluble material weighed 5 g.

2-Ethyl-2-methyl-1,3-diketo-2,3-dihydro-1H-pyrido[3,2,1-*kl*]-phenothiazine (Compound III when R = CH_3; R′ = C_2H_5; Z = S).—(1) Preparation by methylation of "ethylmalonylphenothiazine."[3] Sodium ethoxide was made from 2.3 g. (0.1 g.-atom) of sodium and 200 ml. of commercial absolute ethanol, and 29.5 g. (0.1 mole) of "ethylmalonylphenothiazine" was dissolved in the solution. Addition of 16 g. (0.12 mole) of methyl iodide was followed by heating under reflux overnight. Additional ethoxide prepared from 0.41 g. (0.018 g.-atom) of sodium and 50 ml. of ethanol, and 2.3 g. (0.016 mole) of methyl iodide was then added, and the solution was heated an additional 24 hr. Most of the ethanol was then distilled on the steam bath at reduced pressure, the residue taken up in benzene, filtered from crude "ethylmalonylphenothiazine" (this recrystallized from ethanol to give 3 g. of pure starting material), and extracted with aqueous sodium carbonate to remove unchanged starting material. (Acidification gave 2.6 g. of starting material.) Removal of the benzene by distillation *in vacuo* left 24.1 g. of residual solid of m.p. 138–140°. This was dissolved in boiling ethanol, charcoaled, filtered, and cooled to yield 12 g. of yellow solid, whose m.p. was unchanged by further recrystallization or by treatment with boiling aqueous-methanolic hydrochloric acid in the cleavage outlined below. This then was pure C-methylation product.

The mother liquors were evaporated down and the residues combined and heated under reflux for 3.5 hr. with enough of a solution made up of equal volumes of methanol and concentrated hydrochloric acid to dissolve them. Distillation of solvents from the acidic solution yielded 6 g. of residue, from which 2.5 g. of "ethylmalonylphenothiazine" was obtained by extraction from benzene solution by aqueous sodium carbonate, and subsequent acidification.

(2) Preparation by ethylation of "methylmalonylphenothiazine." Fifty grams (0.175 mole) of "methylmalonylphenothiazine" was dissolved in 500 ml. of commercial absolute ethanol containing the sodium ethoxide from 4.1 g. (0.178 g.-atom) of sodium. Thirty grams (0.19 mole) of ethyl iodide was added with stirring, and the solution was heated under reflux for 24 hr. Distillation of solvent and subsequent partitioning of the residue between benzene and aqueous alkali led to isolation of 43.7 g. of brown grease by evaporation of the benzene. This was distilled at 209–213° (0.3 mm.), and the 30 g. of distillate was recrystallized from absolute ethanol twice, giving 4.7 g. of C-ethylated product m.p. 141–144°, undepressed on admixture with the product of methylation of "ethylmalonylphenothiazine" prepared as given above, under method 1.

When the combined mother liquors were heated under reflux for 24 hr. with 400 ml. of a solution of equal volumes of ethanol and of concentrated hydrochloric acid for 24 hr., and partitioned between benzene and 0.5 *N* sodium hydroxide after distillation of most of the ethanol and acid, acidification of the basic aqueous solution gave 15.3 g. of analytically pure "methylmalonylphenothiazine," representing 16 g. of O-alkylated product present before hydrolysis. The non-acidic fraction was 6.3 g. of presumably somewhat impure C-alkylation product.

2-Bromo-2-ethyl-1,3-diketo-2,3-dihydro-1H-pyrido[3,2,1-*kl*]-phenoxazine ("2-Bromoethylmalonylphenoxazine").—Bromination of 5 g. of "ethylmalonylphenoxazine"[1,3] (0.018 mole) dissolved in 150 ml. of carbon tetrachloride with 2.9 g. (0.018 mole) of bromine in carbon tetrachloride (see *e.g.*, ref. 1) gave, after extraction with 0.5 *N* aqueous sodium hydroxide, 4.8 g. (75%) of brownish solid, m.p. 126–129°. After two recrystallizations from anhydrous ethanol this gave a yellow product, m.p. 128–129°. Starting material could be recovered from the alkaline extract in nearly theoretical amount.

Anal. Calcd. for $C_{17}H_{12}BrNO_3$: mol. wt., 358.20; C, 57.00; H, 3.36. Found: C, 56.91; H, 3.39.

2-Ethyl-2-2′-cyanoethyl-1,3-diketo-2,3-dihydro-1H-pyrido-[3,2,1-*kl*]phenothiazine.—Twenty grams (0.068 mole) of "ethylmalonylphenothiazine," 80 ml. (excess) of acrylonitrile, 50 ml. of peroxide-free dried dioxane, and 10 ml. of a 38% solution of trimethylbenzylammonium hydroxide[11] were heated under reflux with stirring for 4.5 hr. The resulting solution was partitioned between aqueous sodium carbonate solution and chloroform. Acidification of the aqueous solution gave 9 g. of recovered "ethylmalonylphenothiazine," and evaporation of the dried chloroform phase gave 11.1 g. of solid. This was recrystallized twice from ethyl acetate giving after the first recrystallization 4.2 g. of a product of m.p. 168–170°, after the second a yellow product of m.p. 174–175.5°, not raised on recrystallization.

Anal. Calcd. for $C_{20}H_{16}N_2O_2S$: C, 69.00; H, 4.63. Found: C, 69.28; H, 4.64.

When heated with equal volumes of methanol and concentrated hydrochloric acid for 2 hr. under reflux, the cyanoethylated compound gave little alkali-soluble material, but the recovered material had m.p. 162–172°. One recrystallization from ethyl acetate gave material with acceptable m.p. undepressed on admixture with the pure starting material.

O-Alkylation of "Malonyl-Compounds" in Table I. Example of Procedure A.—The sodio derivative was prepared by stirring "ethylmalonylphenothiazine" with the theoretical amount of 1 *N* aqueous sodium hydroxide, adding a slight excess of alkali if necessary to dissolve the solid to form an opalescent solution. The filtered yellow solution was concentrated on a steam bath at the water pump. The resulting glassy solid was dissolved in anhydrous ethanol, approximately two volumes of benzene was added, and the solution was again evaporated. This solution in ethanol and evaporation with excess benzene was repeated if necessary to produce a friable "foamed-up" solid. The resulting sodio salt appeared quite stable in a stoppered bottle, and dissolved rapidly in ethanol.

t-Butyl alcohol was dried over calcium hydride, and 31.7 g. (0.1 mole) of the above "sodio ethylmalonylphenothiazine" was added to it, followed by 7.6 g. (0.053 mole) of 2-chloroethyldimethylamine hydrochloride, which had previously been powdered and dried at 80° (0.1 mm.). The resulting mixture was stirred under reflux for 3 days. Most of the solvent was then removed on the steam bath *in vacuo*. The residue was partitioned between ether containing about 10% by volume of ethanol, and 1 *N* aqueous sodium hydroxide. Acidification of the alkaline aqueous solution gave 10.5 g. of recovered "ethylmalonylphenothiazine."

Extraction of the ethereal solution twice with an excess of 0.5 *N* aqueous hydrochloric acid, treating the acidic aqueous solution with base, and ether extraction of the resulting oil, led, after removal of the solvent from the dried solution, to 8.35 g. of a dark oil. This was converted to its hydrochloride with ethanolic hydrochloric acid, and that recrystallized from ethanol–ethyl acetate–ether to give yellow platelets of m.p. 208–211°. Another recrystallization from the same solvents gave 4.98 g. of greenish yellow solid, m.p. 216–220.5° (bubbles).

O-Alkylation of "Malonyl Compounds" in Table I. Example of Procedure B.—A solution of 11.5 g. (0.073 mole) of 3-chloro-N,N-dimethylaminopropylamine in 10 ml. of water was made alkaline with 10 g. of anhydrous potassium carbonate, extracted with benzene, made more alkaline with an equal volume of 50% aqueous sodium hydroxide, and again extracted with benzene. The combined benzene layers were dried briefly over Drierite, and added to preformed (see procedure A) "sodio ethylmalonylphenothiazine" dissolved in ethanol, and heated under reflux for 4 days. The work-up was as under procedure A.

O-Alkylation of "Malonyl-Compounds" in Table I. Example of Procedure C.—A solution of 1.18 g. (0.051 g.-atom) of sodium in 50 ml. of commercial absolute ethanol had 15 g. (0.051 mole) of "ethylmalonylphenothiazine" added. The base obtained from 14.8 g. (0.059 mole) of 1-3′-chloropropyl-4-methylpiperazine dihydrochloride (analogously to the method used in procedure B) was added dissolved in 250 ml. of benzene, the solution was heated for 2 days, and worked up as above.

1-Methyl-3-ethyl-4-[3-(4-methyl-1-piperazino)propyloxy]-2-pyridone (Compound VI).—This substance was prepared from

(11) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **65**, 23 (1943).

20.3 g. (0.1 mole) of 1-methyl-3-ethyl-4-hydroxy-2-pyridone (V) "ethylmalonylmethylaniline" by procedure C above. The base prepared by sodium carbonate treatment of the hydrochloric acid extract was distilled in a wide-path distilling apparatus, discarding a little lower boiling material and collecting 30.17 g. of a liquid boiling at 181–208° (0.005 mm.). This solidified and had m.p. 73–76°, after one recrystallization from hexane. It was converted to its hydrochloride in ethanol, and recrystallized from ethanol–ether for analysis (m.p. 244–246°). It was very hygroscopic especially when wet with solvent. Thirty grams (72%) was obtained.

Anal. Calcd. for $C_{20}H_{31}Cl_2N_3O_2$: C, 57.69; H, 7.51. Found: C, 57.75; H, 7.30.

1-Methyl-3-ethyl-3-bromo-2,4-diketo-1,2,3,4-tetrahydroquinoline (Compound VII) and 1-Methyl-3-ethyl-3,6-dibromo-2,4-diketo-1,2,3,4-tetrahydroquinoline (Compound VIII).—A part solution–part suspension of 40.6 g. (0.2 mole) of finely ground 1-methyl-3-ethyl-4-hydroxy-2-quinolone ("ethylmalonylmethylaniline," Compound V) in 520 ml. of acetone-free methanol was stirred and treated with 37 g. (0.23 mole) of bromine dissolved in 100 ml. of carbon tetrachloride, added in about 30 sec. The initial rapid uptake of bromine slowed near the end of the addition. After 10 min., the solvents were evaporated at the water pump (steam bath). Some bromine was evolved. The residual oil was then dissolved in the minimal amount of boiling ethanol, diluted with ether, and extracted with 0.5 *M* aqueous sodium carbonate. Acidification of the carbonate solution gave 26 g. of precipitated acidic material, m.p. 161–186°. (The starting material had m.p. 184–186°.)

Concentration of the carbonate-extracted ethereal solution left 28.5 g. of a yellow oil, which soon solidified. This was washed with a little hexane, and then had m.p. 123–154°. It was recrystallized from 1.2 l. of hexane, giving 10.8 g. of yellow crystals, m.p. 148–152°. Concentration of the hexane solution to 300 ml. and storage at −14° led to crystallization of 12.2 g. of yellow solid, m.p. 84–88.5°. A third crop of m.p. 69–76° could be obtained by replacement of the hexane by *ca.* 20 ml. of anhydrous ether. The above mentioned second crop was recrystallized twice more from hexane (cooling to −14°) for analysis, m.p. 86–90°. It gave a satisfactory analysis for the mono bromo compound.

Anal. Calcd. for $C_{12}H_{12}BrNO_2$: C, 51.08; H, 4.29. Found: C, 50.80; H, 4.61.

The highest melting first crop above was recrystallized from hexane, cooling to 4°. It had m.p. 152–158°.

Anal. Calcd. for $C_{12}H_{11}Br_2NO_2$: C, 39.91; H, 3.07. Found: C, 40.45; H, 3.17.

1-Methyl-3-dimethylamino-3-ethyl-6-bromo-1,2,3,4-tetrahydroquinoline-2,4-dione (Compound IX).—This was prepared by mixing ethereal solutions of the bromo compound VIII (above) and excess of dimethylamine, and allowing the solution to remain for 2 days. A yield of 85% of the solid base was obtained, m.p. 120–122° after recrystallization from ethanol, and 5% of theory of an acidic material was also obtained. The base was a yellow solid.

Anal. Calcd. for $C_{14}H_{17}BrN_2O_2$: C, 51.70; H, 5.26. Found: C, 51.93; H, 5.11.

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1,2,4-Triazoles. VII.[1a] Dimethylformamide in the Synthesis of *s*-Triazoles and a Facile Opening of This Ring System

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Dimethylformamide has been shown to react with benzhydrazide benzenesulfonate yielding 4-benzamido-3-phenyl-*s*-triazolium benzenesulfonate (I), 1-benzoyl-4-formamidobenzhydrazidine (II), and 1-benzoyl-2-formylhydrazine, together with related products formed by self-condensation of benzhydrazide. Treatment with dilute alkali under mild conditions readily effected ring opening of the triazole nucleus of I, forming II; II can be converted into I with benzenesulfonic acid, and into 4-benzamido-3-phenyl-*s*-triazole (IV) with other cyclization agents.

Amides, and especially formamides, have proved particularly useful as a source of a one-carbon fragment bearing hydrogen in the synthesis of various nitrogen-containing heterocycles. It has been shown recently that dimethylformamide is protonated on the oxygen atom by strong acids[2] and that the oxygen atom is also the site of reaction with methyl sulfate,[3] phosphoryl chloride, and thionyl chloride,[4] and that with primary amines substituted amidines are formed. Because the *s*-triazole system may be regarded as incorporating the structural elements of an amidine, these results indicated that dimethylformamide might be a useful reagent for condensation with suitable intermediates in a synthesis of this ring system. This paper describes an application of dimethylformamide in the synthesis of 3,4-disubstituted *s*-triazoles with no substituent on carbon 5; this method is thus complementary to the ring closures of hydrazidines with ortho esters or acidic cyclodehydration agents that yield 1,3-disubstituted and 1,3,5-trisubstituted *s*-triazoles.[5] The usual methods employed in the synthesis of 4-substituted *s*-triazoles lead directly to the *s*-triazole system with substituents in the 3-, 4-, and 5-positions.[6]

Benzhydrazide benzenesulfonate and dimethylformamide at reflux temperature underwent reaction with formation of 4-benzamido-3-phenyl-*s*-triazolium benzenesulfonate (I) and 1-benzoyl-4-formamidobenzhydrazidine (II) as the major products. The addition of concentrated sodium hydroxide solution, followed by mineral acid, was essential for the isolation of I and this isolation procedure probably exerted a salting-out effect on the benzenesulfonate. High temperatures (about 155°) were necessary for the condensation to occur. At 100° the only basic product isolated from the re-

(1) (a) Part VI. P. J. Nelson and K. T. Potts, *J. Org. Chem.*, **27**, 3243 (1962). Part of this material has been published as a Preliminary Communication in *Chem. Ind.* (London), 2049 (1961). (b) Present address.

(2) G. Fraenkel and C. Franconi, *J. Am. Chem. Soc.*, **82**, 4478 (1960).

(3) H. H. Bredereck, R. Gompper, H. Rempfer, K. Klemm, and H. Keck, *Chem. Ber.*, **92**, 329 (1959).

(4) (a) H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, **42**, 1659 (1959); see also H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *ibid.*, **42**, 1653 (1959); (b) G. Tosolini, *Chem. Ber.*, **94**, 2731 (1961).

(5) A. Pinner, *Ber.*, **27**, 997 (1894); M. R. Atkinson and J. B. Polya, *J. Am. Chem. Soc.*, **75**, 1471 (1953); M. R. Atkinson and J. B. Polya, *Chem. Ind.* (London), 3319 (1954); D. Jerchel and R. Kuhn, *Ann.*, **568**, 185 (1950); W. Reid and F. Muller, *Chem. Ber.*, **85**, 170 (1952).

(6) K. T. Potts, *Chem. Rev.*, **61**, 87 (1961).