[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

ANTIMALARIALS. α,β-DIMORPHOLINYL KETONES AND RELATED COMPOUNDS[1, 2]

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This work stemmed from the observation that 1,2-dibenzoyl-1-dibutylaminoethylene (I) retarded appreciably the growth of parasites in ducks infected with *Plasmodium lophurae*[4, 5] (1).

$$C_6H_5COCH{=}C(N(C_4H_9)_2)COC_6H_5$$

I [SN[6]88; Q[7] = < 0.015]

Other analogs of this compound, made subsequently for comparative tests, seemed also to be slightly active,[5] especially the morpholinyl analog (2).[5]

To study the effect of deletion of the γ-carbonyl group from this type (I) samples of known α-(tertiary-amino)chalcones (benzalacetophenones) of the type II (4) were prepared and tested, and of these the α-diethylamino compound

[1] (a) The larger portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia. Some parts of the work were supported by a subsequent grant-in-aid from the National Institutes of Health.

(b) The bulk of the work reported in this paper followed from the discovery of antimalarial activity in the compounds of the type I, II, and III through tests on samples submitted from this laboratory during the summer of 1942 to the Lilly Research Laboratories and to the National Institutes of Health. Since an extension of the studies on the type II and III compounds had been started earlier by Cromwell in 1940 [(4b), (4c), cf. (7)] this program (under O.S.R.D.) was limited to the development of the antimalarial lead, by way of synthesis of analogous compounds specifically for antimalarial tests.

[2] Acknowledgment: The synthesis of certain of the compounds reported were carried out by (a) P. S. Bailey, (b) J. A. Freek, (c) A. G. Howe, (d) J. F. Tinker, and (e) W. L. Yost.

[3] Present locations: (a) General Aniline and Film Corp., Easton, Pa., (b) National Institutes of Health, Bethesda, Md., (c) Deceased, (d) Southern Research Institute, Birmingham, Ala., (e) S. E. Massengill Co., Bristol, Tenn., (f) Chemical Abstracts, Columbus, Ohio, (g) Richmond Medical College, Richmond, Va., (h) Smith, Kline, and French Laboratories, Philadelphia, Pa.

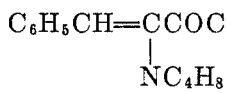
[4] Carried out at the Lilly Research Laboratories.

[5] This compound is listed as "inactive" according to the standards set up in the Survey monograph [see (3)].

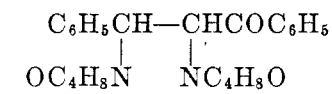
[6] The SN number (Survey number) identifies the drug in the Wiselogle Monograph [see (3)].

[7] Quinine equivalents [see (3)] unless otherwise specified were determined against *P. gallinaceum* in the chick, at the National Institutes of Health under the direction of Dr. G. Robert Coatney.

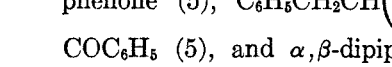
showed indication of slight activity,[5] as also did the α-morpholinyl compound (II).[5]



II [SN 1623; Q = < 0.03]



III [SN 2623; Q = 0.1]

Related compounds in this field, α-mono-(tertiary-amino)-β-phenylpropiophenone (5),  , the β-analogs, , and α,β-dipiperidyl-β-phenylpropiophenone (an analog of III) (4a, 6), were inactive, but α,β-dimorpholinyl-β-phenylpropiophenone (III) (4c) was found to be definitely "active" (3), being one-tenth as active as quinine against *P. gallinaceum* in the chick.[7, 8]

Since antimalarial activities of Q = 0.015–0.06 were found in numerous other compounds of the type (III), whereas no activity was observed in analogs carrying tertiary-amino groups other than morpholine, efforts were directed toward the substitution of groups in one or both phenyl nuclei. Thirty new α,β-dimorpholinyl-β-phenylpropiophenones have been made, and are listed in Table I. These involve as substituent groups, alkyl, phenyl, halogen, alkoxyl, nitro, acetamido, and carbethoxyamino; and of these, nine derivatives proved to be definitely "active" but none was as active as the first of the type to be tested, namely, III itself.

The dimorpholinyl ketones were made from the corresponding chalcones (Table II) by the action of morpholine on the dibromides (Table III); [*cf.*, (7)]. Only in the parent series and in one other to be reported later, were the stereoisomers obtained, but in several cases there was observed the formation of the α-morpholinylchalcone (*cf.* II). The aryl substituent influenced the relative yields of the latter type compound in about the way that would be expected. Where the 4′-substituent (in the phenyl next to the keto group) was alkyl, phenyl, acetamido, carbethoxyamino, or alkoxyl, the dimorpholinyl ketone of type III was the only product isolated except in the single case of the 4′-phenyl compound where, along with a 91% yield of the expected product, there was obtained an 8% yield of the α-morpholinylchalcone of the type II. On the other hand, a 4′-chlorine or bromine decreased the yields of the dimorpholinyl product and increased the yields of the α-morpholinylchalcone to 31% and 38% respectively; and the 4′-nitro group brought the yield of the α-morpholinylchalcone up to 81% and lowered the yield of the dimorpholinyl ketone to 12%. These results are explainable in terms of electron displacement toward the *para* halogen or *para* nitro group and the increased stabilization of the α,β-unsaturated ketone system of the α-morpholinylchalcone structures.

The nineteen new chalcones listed in Table II were obtained in widely varying yields. Some of them, especially those carrying a *para*-nitrogen, were made with

[8] Tested against *P. lophurae* in the duck (Q = 0.03) at the Johns Hopkins Medical School under the direction of Dr. E. K. Marshall, Jr.

TABLE I

THE α,β-DI-(TERT-AMINO)-β-PHENYLPROPIOPHENONES AND THE α- (AND β-)-(TERT-AMINO) BENZALACETOPHENONES (CHALCONES)

(Ar-C-C-CO-Ar')

SN[a] (OR DR)	SUBSTITUENTS[b]	PREP. METHOD	REACT. TIME (HRS.)	YIELD, %	M.P., °C. (CORR.)	NO.[c] IN TABLE IV
	A. THE α,β-DIMORPHOLINYL-β-PHENYLPROPIOPHENONES (TYPE III)					
3296	4'-Methyl	A[g]	2	24[e]	165–166	1
3295	4'-Isopropyl[f]	E	1	25[e]	176–177	2
4048	4'-*tert*-Butyl	A	1	79	176–177	3
4049	4'-Cyclohexyl	A[g]	1	30[e]	190–191	4
4045	4'-($CH_2CH_2C_6H_5$)	A	3	22[e]	175–176	5
—	4'-Phenyl[h]	C	24	91	184–186	6
6637	4'-Chloro[h]	C	24	61	162–163	7
4047	4'-Bromo[h]	C	10	52	158–159	8
—	4'-Nitro[h]	C	12	12	166–167	9
15,487	4'-$NHCOCH_3$	B, J	10	36[e]	201–202	10
15,665	4'-$NHCOOC_2H_5$	B	10	80	182–183	11
3110	4'-Methoxy	B[g]	16	58[i]	167–168.5	12
3639	4'-Ethoxy	A	3	86	173–174	13
4671	4'-*n*-Propoxy	B	24	63[i]	157[d]	14
4676	4'-Isopropoxy	B	24	89	157	15
4125	4'-*n*-Butoxy	B[g]	48	44[i]	162–163	16
3642	4'-Phenoxy	A	3	54	153–155	17
3759	4-Isopropyl	A	3	43[i]	181–183[d]	18
6637	4-Chloro	A	1	15[i]	165–165.5	19
3637	3-Methyl	A	2.5	40[e]	173–174	20
3093	3-Nitro	B[g]	2	45[j]	178	21
9169	2-Methoxy	A	3	70	175–176	22
3638	2',5'-Dimethyl	A	3	31[e]	163–165[d]	23
3540	2',4'-Diisopropyl	A	1	63	147–148	24
4669	3',4'-Dichloro	B	B	23[e]	164–165	25
4903	5-Bromo-2',4'-dimethoxy[13]	A[f]	—	—[f]	166–166.5	26
4677	4,4'-Dimethoxy	A	1.5	41[i]	178–179	27
4906	4'-Chloro-3'-methyl	B	3	16[e]	169–170	28
3641	4'-Isopropyl-4-methoxy	A	3	69	174[d]	29
4667	2',4',6'-Trimethyl	A	3	47	179–180	30
	B. THE α,β-DIPIPERIDYL-β-PHENYLPROPIOPHENONES					
—	3-Methylpiperidyl	B[n]	10	7	144–146	31
9020	4-Methylpiperidyl	B[n]	10	61	151[p]	32
3112	4'-Methoxy	B[g]	4	58	143–145.5	33
4063	4'-Phenoxy	A	2	81	165	34
	C. AN α,β-BIS-(TETRAHYDROISOQUINOLYL)-β-PHENYLPROPIOPHENONE					
4064	4'-Methoxy	B	—	40[i]	152–153	35

TABLE I—*Concluded*

SN[a] (OR DR)	SUBSTITUENTS[b]	PREP. METHOD	REACT. TIME (HRS.)	YIELD, %	M.P., °C. (CORR.)	NO.[c] IN TABLE IV
D. OTHER α,β-DI(SUBSTITUTEDAMINO)-β-PHENYLPROPIOPHENONES						
6416	β-Anilino-α-benzylmethylamino	F	24	24[i]	133–134	36
5031	α-Benzylmethylamino-β-morpholinyl	F	10	30[i]	159	37
4678	α-Benzylmethylamino-β-methylanilino	F	9	68[i]	145	38
4904	β-Anilino-α-morpholinyl	G[g]	0.3	85	187–189	39
4902	β-Methylanilino-α-morpholinyl	G	5	53	168–169	40
E. THE α-MORPHOLINYLBENZALACETOPHENONES (CHALCONES) (TYPE II)						
1623	None[f]	H	—[f]	—[f]	93	41
—	4′Phenyl[k]	D	24	8	142–144	42
3549	4′-Chloro[k]	D	24	31	108	43
6975	4′-Bromo[k]	D	10	38	105–106	44
—	4′-Nitro[k]	D	12	81	147–148	45
F. THE β-(TERT.-AMINO)BENZALACETOPHENONES (TYPE V)						
3548	β-Morpholinyl[l]	I[m]	—	76	94–95	46
3260	β-Piperidyl	I	—[f]	52[f]	80–81	47
			—[f]	—	101–102	48

[a] Survey Number (see footnote[6]); the five-digit numbers are DR = drug repository, National Institutes of Health. [b] For quinine equivalents see (3). [c] Refers to analyses listed in Table IV. [d] Melts with decomposition. [e] These yields refer to highly purified material. [f] See experimental section. [g] Absolute ethanol was used as the reaction solvent. [h] For the data on the other product isolated from this reaction, see D. [i] Yield after one recrystallization. [j] Yield after several washings with ethanol. [k] For the data on the other product isolated from this reaction, see C. [l] Originally prepared (4c) by heating dibenzoylmethane with excess morpholine; m.p. 96–97°. A mixture melting point of samples prepared in the two ways showed no depression. Acid hydrolysis gave dibenzoylmethane. [m] Distilled β-methoxybenzalacetophenone was used as starting material. [n] Allowed to stand overnight in the refrigerator. [p] Solubility: in water at 25°, 0.05 g. per 100 ml.; at 90°, 0.1 g. per 100 ml.; in 3 *N* HCl at 25°, 1.0 g. per 100 ml.

the high antibacterial activity of benzalacetophenone and dibenzoylethylene in mind [*cf.* (8)].[9]

Absorption spectra of six of these compounds[10] over the wavelength range

[9] The following tests on substituted chalcones were carried out at the Lilly Research Laboratories. The 4-dimethylamino- and 4-diethylamino-chalcones and their 4′-ethoxycarbamino and 4′-acetamido derivatives showed little or no significant bactericidal, bacteriostatic or fungicidal activity. The 4-dimethylaminochalcone and three compounds of Table II (nos. 62, 64, 65) showed no significant antihistamine activity. The 4-dimethylaminochalcone and its 4′-ethylcarbamino derivative showed negligible ergotrate activity, and were not effective against tuberculus bacilli *in vitro*.

[10] The absorption spectra and interpretations of them were made by Dr. Henry Hemmindinger of the General Aniline and Film Corp., Easton, Penna.

600–220 mμ are shown in Figures 1 and 2 [*cf.* also (9)]. Over the concentration range studied there was no dependence of extinction coefficient on concentration.

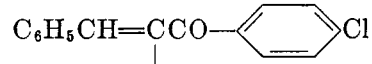
TABLE II

THE CHALCONES: ArCH=CHCOAr′

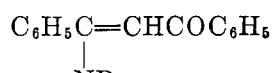
SUBSTITUENT	PREP.[a] METHOD	REACT. TIME (HRS.)	CRYST. FROM[b]	YIELD, %	M.P. OR B.P., C. (CORR.)	NO. IN TABLE IV
4′-Cyclohexyl	A	—	EtOAc	90	124[i]	49
4′-$CH_2CH_2C_6H_5$	A	6	Ethanol	77	117[i]	50
4′-$NHCOCH_3$ (14)	A	2	Ethanol	63	160–161[k]	51
4′-$NHCOOC_2H_5$	A[c]	1	Ethanol	81	143–145[i]	52
4′-$NHCONH_2$	A	0.5	Diox. EtOH	53	217–218[k]	53
4′-*n*-Propoxy	A	2	Ethanol	71	76[i]	54
4′-Isopropoxy	A	3	Ethanol	23[d]	87[i]	55
4′-*n*-Butoxy	A	3	Ethanol	98	67–68[j]	56
4-$N(C_2H_5)_2$[f]	D[e]	3	[f]—	56	260–265[g, l]	57
2′,5′-Dimethyl[f]	B	2.5	[f]—	77	203–204[h]	58
3′,4′-Dichloro	A	1	Abs. EtOH	85	115–116[i]	59
4′-Chloro-3-methyl	A	2	Ethanol	81	106[i]	60
4′-Isopropyl-4-methoxy	A	2.3	Ethanol	89	71–72[j]	61
4′-$NHCOCH_3$-4-$N(CH_3)_2$	C	0.5	Acet. CH_3OH	54	204–205[k]	62
4′-$NHCOCH_3$-4-$N(C_2H_5)_2$	C	0.5	Butanone	75	157–158[k]	63
4′-$NHCOOC_2H_5$-4-$N(CH_3)_3$	D	2	Butanone	67	188–189[l]	64
4′-$NHCOOC_2H_5$-4-$N(C_2H_5)_2$	D	3	Butanone	68	157–159[l]	65
4′-$NHCONH_2$-4-$N(CH_3)_2$	A	1	Acet. EtOH	26	218–220[l]	66
4′-[$N{=}CHC_6H_4N(CH_3)_2$-(*p*)]-4-$N(CH_3)_2$	E	0.2	Acet. EtOH	—	223–225[l]	67

[a] See procedures in experimental section. [b] Solvent abbreviations: EtOAc = ethyl acetate; diox. = dioxane; EtOH = ethanol; acet. = acetone; but. = butanone. [c] Prepared also by the action of ethyl chlorocarbonate upon 4′-aminochalcone. [d] Also a 16% recovery of 4′-isopropoxyacetophenone; b.p. 78°/6 mm. [e] The reaction mixture was worked up according to B. [f] Oils. [g] B.p. at 7 mm. [h] B.p. at 1 mm. [i] Colorless. [j] Pale yellow. [k] Yellow. [l] Orange.

Among the few α-morpholinylchalcones (type II) studied, one, the 4′-chloro compound (IV), showed definite activity (Q = 0.03). The parent compound II



IV



V

was the only other compound of the type tested at comparable dosage and it was "inactive".

The isomeric β-morpholinylchalcone (V) and the β-piperidyl analog [*cf.* (7a)] were also made for comparison, but they were inactive (Q = <0.015); they were prepared by a new and improved method, from $C_6H_5C(OCH_3){=}CHCOC_6H_5$; this is essentially the method of Dufraise and Netter (10) which had been successfully applied to α-bromo-β-methoxychalcone.

In connection with the foregoing studies attempts were made to use substituted morpholines and piperidines in the reaction with chalcone dibromide. A number of mono- and dialkyl-morpholine derivatives were supplied by Dr. W. S. Cottle (11).[11] These were of particular interest in view of the seeming specificity for antimalarial activity of the morpholinyl group in this class of compounds, but unfortunately in our hands none of them gave crystalline prod-

TABLE III

THE CHALCONE DIBROMIDES: ArCHBrCHBrCOAr′

SUBSTITUENT	YIELD, %	CRYST. FROM[a]	M.P., °C. (CORR.)	EMPIRICAL FORMULA	NO. IN TABLE IV
4′-Isopropyl [*cf.* (15)]	91[e]	Acet. CH_3OH	143	$C_{18}H_{18}Br_2O$	68
4′-*tert*-Butyl	77[f]	Abs. EtOH	139.5–142	$C_{19}H_{20}Br_2O$	69
4′-Cyclohexyl	90[f]	—[i]	155–158	—	70
4′-$Ch_2CH_2C_6H_5$	96[e]	Ethanol	130–131	$C_{23}H_{20}Br_2O$	71
4′-Phenyl	90[g]	Acet. EtOH	195–196	$C_{21}H_{16}Br_2O$	72
4′-Chloro	98[f]	$ChCl_3$	192	$C_{15}H_{15}Br_2NO_2$	73
4′-$NHCOCH_3$ (16)[b]	62[f]	Ethanol	176–177[d]	$C_{17}H_{11}Br_2ClNO$	74
4′-$NHCOOC_2H_5$	81[e]	CCl_4	201–202[d]	$C_{18}H_{17}Br_2NO_3$	75
4′-*n*-Propoxy	93[e]	Ethanol	149	$C_{18}H_{18}Br_2O_2$	76
4′-Isopropoxy	48[h]	Ethanol	131	$C_{18}H_{18}Br_2O_2$	77
4′-*n*-Butoxy	62[e]	Ethanol	153–154	$C_{19}H_{20}Br_2O_2$	78
3-Methyl (17)[c]	86[e]	CH_3OH	123–124[c]	$C_{16}H_{14}Br_2O$	79
2-Methoxy	98[e]	Pet.-CCl_4	123–124	$C_{16}H_{14}Br_2O_2$	80
2′,5′-Dimethyl	77[f, i]	Ethanol	103–104	$C_{17}H_{16}Br_2O$	81
2′,4′-Diisopropyl	52[g]	Ethanol	124–125	$C_{21}H_{24}Br_2O$	82
3′,4′-Dichloro	80[e]	CCl_4	166–167	$C_{15}H_{10}Br_2Cl_2O$	83
4′-Chloro-3′-methyl	95[f]	Ethanol	146–147	$C_{16}H_{13}Br_2ClO$	84
4′-Isopropyl-4-methoxy	66[e, h]	CH_3OH	111–112	$C_{19}H_{20}Br_2O_2$	85
4,4′-Dimethoxy	98[e]	Benzene	147–148[d]	$C_{17}H_{16}Br_2O_3$	86

[a] Solvent abbreviations: acet. = acetone; EtOH = ethanol; pet. = petroleum ether. [b] Giua and Bagiella (16) described this compound as yellow prisms of m.p. 175°; our sample was colorless (rectangular prisms). [c] Giua (17) originally prepared this compound and reported the m.p. 127–128°. [d] Melts with decomposition. [e–h] Reaction solvents were [e] Carbon tetrachloride; [f] Chloroform; [g] Chloroform-ether mixture; [h] Absolute ether. [i] Cold ligroin added to precipitate the crude product. [j] Analytical sample not prepared.

ucts in this reaction. Partial success was achieved in the reactions with substituted piperidines.[11] In a series of comparable experiments, piperidine itself gave the α,β-dipiperidyl ketone in 69% yield (purified), and the α,β-bis-(4-methylpiperidyl) analog was obtained in 61% yield; the bis-(3-methylpiperidyl)ketone was obtained in smaller yield (27%), but no satisfactory products were isolated when 2-substituted piperidines were used, namely, the 2-methyl-, 2,4- and 2,6-dimethyl-, and 2,4,6-trimethyl-piperidines. Doubtless steric effects are operating in the latter cases, as would be expected.

[11] The substituted morpholines were furnished by Dr. W. S. Cottle (11) and the substituted piperidines by the C.M.R. group of Columbia University under Dr. R. C. Elderfield.

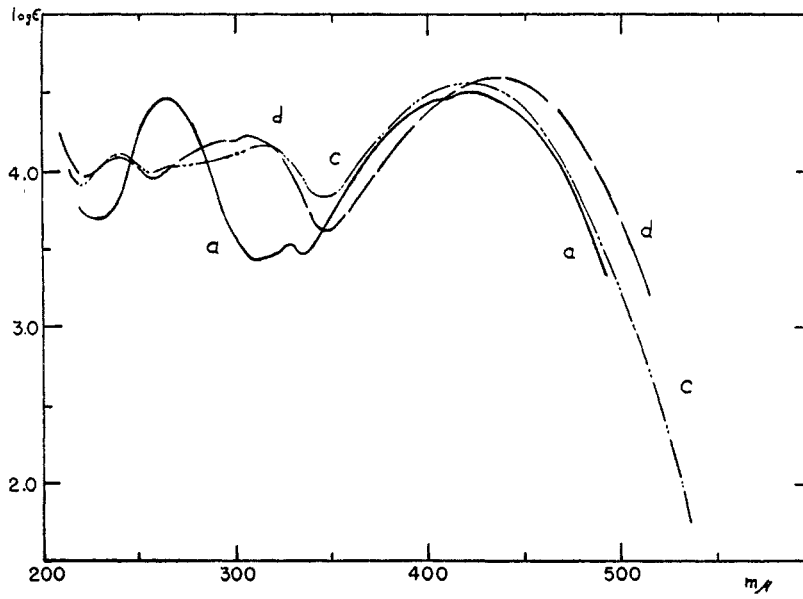


FIG. 1

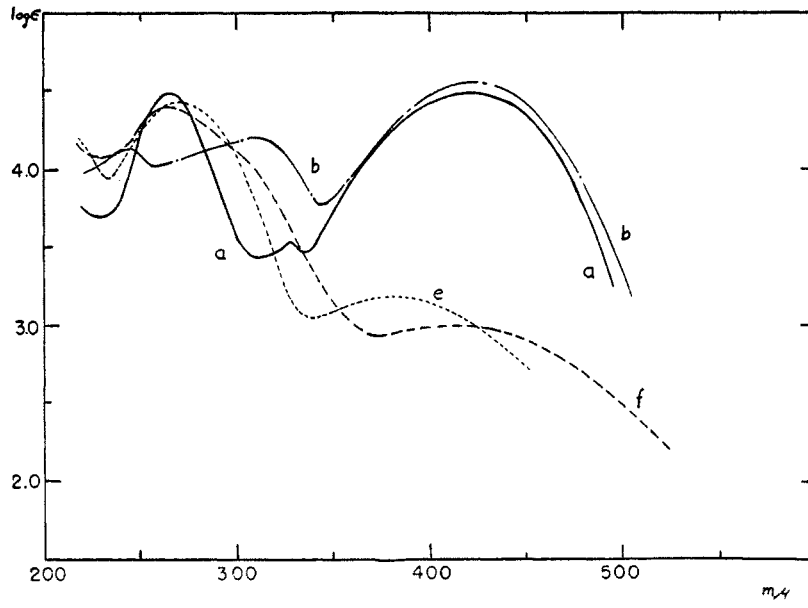


FIG. 2

FIGURES 1–2. ABSORPTION SPECTRA OF SIX CHALCONE DERIVATIVES

(a) ———— (*p*)-$(CH_3)_2NC_6H_4CH{=}CHCOC_6H_5$ [See (9)]

(b) —— · —— · —— (*p*)-$(CH_3)_2NC_6H_4CH{=}CHCOC_6H_4NHCOCH_3$-(*p*) (Table II, No. 62)

(c) —— · · —— · · —— (*p*)-$(CH_3)_2NC_6H_4CH{=}CHCOC_6H_4NHCOOC_2H_5$-(*p*) (Table II, No. 64)

(d) —— —— —— —— (*p*)-$(C_2H_5)_2NC_6H_4CH{=}CHCOC_6H_4NHCOCH_3$-(*p*) (Table II, No. 63)

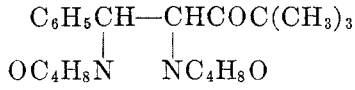
(e) · · · · · · $C_6H_5CH{=}C$(morpholinyl)COC_6H_4Br-(*p*) (Table II, No. 44)

(f) – – – – – – $C_6H_5CH{=}C$(morpholinyl)$COC_6H_4NO_2$-(*p*) (Table II, No. 45)

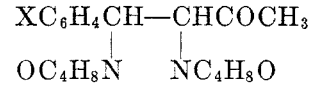
These determinations[10] were made in methanol at concentrations between 0.002 and 0.2 g. per liter and path lengths of 10.0 to 0.1 cm.; the half width of the dispersed beam transmitted by the Cary recording spectrophotometer was less than 0.5 mμ. over the entire range.

Attempts to obtain crystalline diamino ketones using diethyl- and dibutylamines were not successful.

One of the structural changes considered, relative to III, was the deletion of one of the phenyl groups with substitution of hydrogen or of an alkyl. The tertiary-butyl analog (VI) made from benzalpinacolone proved to be active.

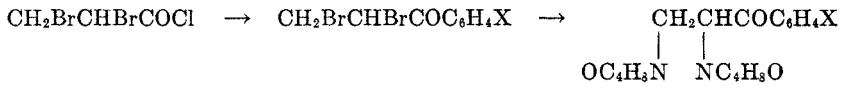


VI [SN 3107; Q = 0.06]



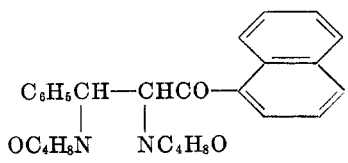
VII (a) X = H; (b) X = *p*-Cl; (c) X = *p*-Br.

The benzylacetone analog and its *p*-chloro and *p*-bromo derivatives (VII), prepared in the usual way [*cf.* (7)], were inactive. The *p*-chloro- and *p*-bromopropiophenone analogs (X) [*cf.* (12)] (also inactive) were prepared by the action of morpholine on the dibromo compounds (IX), which were made by the method of Kohler (13) through α,β-dibromopropionyl chloride (VIII) by the Friedel-Crafts reaction, as shown in VIII–X.

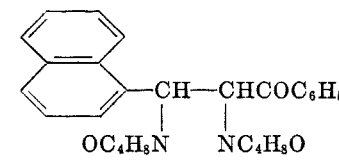


VIII IX X (a) X = *p*-Cl; (b) X = *p*-Br.

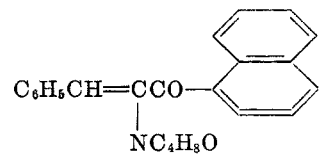
One other major structural variation relative to III was the substitution of a naphthyl residue for one of the phenyls. α,β-Dimorpholinyl-β-phenyl-1-propionaphthone (XI) and its structural isomer (XII) were synthesized, and also the 2-naphthyl analog of XI, and α-morpholinyl-β-phenyl-1-acrylonaphthone (XIII). These compounds were inactive (Q = <0.015).



XI

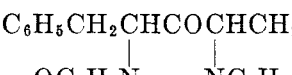


XII

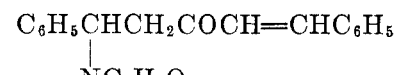


XIII

To test the specificity of the α,β-dimorpholinyl ketone system of III, the α,α′-dimorpholinyl ketone (XIV) was made through 2,4-dibromo-1,5-diphenyl-3-pentanone; it was inactive. An attempt to make the β,β′-dimorpholinyl analog of XIV by the addition of morpholine to dibenzalacetone gave only the monomorpholinyl addition product (XV).

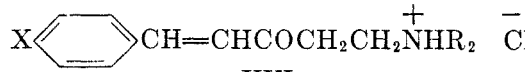


XIV [SN 4670; Q = 0.03]



XV

Incidental to this research several Mannich reactions were carried out on *p*-chloro- and *p*-bromo-benzalacetone; the products (type XVI) were ineffective against malaria.



XVI

Acknowledgment. The absorption spectra reported in Figures 1 and 2 were determined by Dr. Henry Hemmindinger.

EXPERIMENTAL[12]

THE α,β-DI-(TERTIARY-AMINO)-β-PHENYLPROPIOPHENONES AND THE α- (AND β) (TERTIARY-AMINO)CHALCONES

Procedure A. α,β-Dimorpholinyl-β-(m-tolyl)propiophenone. Morpholine (50 g.; 0.52 mole) was added slowly to a stirred solution of 39 g. (0.1 mole) of 3-methylchalcone dibromide (14) in 150 ml. of acetone. The mixture was refluxed for 2.5 hours, cooled to 5°, and filtered to remove morpholine hydrobromide. Evaporation under a stream of air and addition of 50 ml. of ligroin brought about crystallization of the crude product; it was washed with small portions of cold ligroin and with water, and was crystallized once from benzene-ligroin (9:1) mixture and twice from methanol; 16 g. (40%).

Procedure B. 4′-Acetamido-α,β-dimorpholinyl-β-phenylpropiophenone. A mixture of 30 g. (0.07 mole) of 4′-acetamidochalcone dibromide, 30.5 g. (0.35 mole) of morpholine, and 400 ml. of acetone was allowed to stand at room temperature for 10 hours. Filtration gave 23 g. (97%) of morpholine hydrobromide. Concentration of the yellow filtrate under reduced pressure, slurrying with water and filtering, gave 31 g. of yellow solid; m.p. 160–164°. This was digested with 400 ml. of boiling ligroin and filtered while hot (29 g.; m.p. 165–170°); the process was repeated with boiling 90% ethanol (13 g.; m.p. 194–196°). Recrystallization from 400 ml. of absolute ethanol gave 11 g. (36%); pale yellow needles; m.p. 199–201°.

Procedure C. 4′-Bromo-α,β-dimorpholinyl-β-phenylpropiophenone. Morpholine (22 g.; 0.25 mole) was added to a suspension of 22 g. (0.05 mole) of 4′-bromochalcone dibromide in 250 ml. of acetone, with cooling. The resulting orange solution was allowed to stand at room temperature for 10 hours, filtered from the almost theoretical yield of morpholine hydrobromide, and concentrated under reduced pressure; the resulting orange precipitate was washed with water, slurried with 400 ml. of petroleum ether, and filtered; 14 g. (52%).

Procedure D. 4′-Bromo-α-morpholinylchalcone. The final petroleum ether filtrate (above) upon evaporation under reduced pressure gave 7 g. (38%) of orange solid. Two recrystallizations from ethanol and three from hexane gave a pure product; orange rectangular prisms.

Procedure E. α,β-Dimorpholinyl-β-phenyl-p-isopropylpropiophenone. Morpholine (30 g.; 0.34 mole) was added to a stirred suspension of 27 g. (0.066 mole) of 4′-isopropylchalcone dibromide in 200 ml. of absolute ethanol, and the mixture was stirred at 35° for one hour. Cooling to 0° gave an orange precipitate which was washed successively with a little cold ethanol and water; 12 g.; m.p. 158–163°. Recrystallization from ethanol gave 7 g. (25%); very pale yellow solid.

[12] All melting points are "corrected".

Procedure F. α-(Benzylmethylamino)-β-N-methylanilino-β-phenylpropiophenone. A mixture of 12.3 g. (0.03 mole) of β-(benzylmethylamino)-α-bromo-β-phenylpropiophenone (18), 30 ml. of absolute ethanol, and 6.3 g. of methylaniline was warmed slightly to dissolve all of the materials; it was allowed to stand at room temperature for 9 hours and was cooled. The resulting precipitate was crystallized from 800 ml. of methanol; 8.9 g. (68%); m.p. 144–145°.

Procedure G. β-N-Methylanilino-α-morpholinyl-β-phenylpropiophenone. A mixture of 25 g. of α-bromo-β-morpholinyl-β-phenylpropiophenone (5), 15.5 g. of methylaniline, and 55 ml. of methanol was refluxed for 5 hours. Cooling precipitated 14 g. (53%); m.p. 137–142°.

Procedure H. α-Morpholinylchalcone [*cf.* 4c] was prepared without isolation of intermediates as follows: Bromine (54 g.; 0.337 mole) was added dropwise under cooling to a stirred solution of 70 g. (0.336 mole) of chalcone in 250 ml. of absolute ethanol, and one equivalent of sodium ethoxide (from 7.7 g. of sodium and 100 ml. of ethanol) was added. After refluxing for one hour and cooling, 44 g. of morpholine was added and the mixture was allowed to stand overnight. A second equivalent of sodium ethoxide was added and the mixture was refluxed for two hours. Concentration under reduced pressure and washing the orange precipitate with water gave 60 g. (61%); m.p. 89–93°.

Procedure I. A new higher-melting form of β-piperidylchalcone. A mixture of 10 g. of distilled β-methoxychalcone (19, 20), 8 g. of piperidine, and 40 ml. of ethanol was refluxed for fifteen minutes. The product, isolated by addition of water, melted at 101–102°; it was hydrolyzed by 25 ml. of 80% ethanol and 0.3 ml. of conc'd hydrochloric acid (refluxing for 15 minutes), to dibenzoylmethane (identified by mixture m.p.).

The *lower-melting form*, evidently identical with that reported by André (21), was obtained in an experiment carried out several years later, as follows: A solution of 5.75 g. (0.25 mole) of sodium in 100 ml. of methanol was added to a stirred suspension of 46 g. (0.125 mole) of chalcone dibromide in 100 ml. of methanol. The mixture was refluxed for one hour, allowed to cool, treated with 32 g. (0.375 mole) of piperidine, refluxed for forty-five minutes, and poured into water. The partly crystalline precipitate was washed with water, dried, and slurried several times with petroleum ether; 19 g. (52%) of pale yellow solid; m.p. 80–81°. Recrystallization from ethyl acetate-petroleum ether mixture did not change the melting point. André (21) reported the m.p. 81°.

Repetition of the first preparation from distilled β-methoxychalcone gave the higher-melting form (m.p. 101–102°).

Seeding the lower-melting form in solution or in the pulverized solid form caused conversion to the higher-melting form, but attempts to bring about change in the opposite direction were unsuccessful.

5(?)-Bromo-2,4-dimethoxy-α,β-dimorpholinyl-β-phenylpropiophenone (Table I, No. 26)[13] was made from the crude non-crystalline product of the bromination of 2′,4′-dimethoxychalcone (22) in 4:1 carbon tetrachloride-ether mixture at 10°. Purification of the crude product gave only a very small yield of pure compound which contained halogen. It is evident that the desired compound, doubtless the main product, was eliminated in the purification procedure and the much less soluble by-product (brominated in the nucleus) was the one isolated. The exact location of the bromine (assumed) was not checked by direct evidence.

4′-Acetamido-α-bromochalcone. A mixture of 30 g. (0.07 mole) of 4′-acetamidochalcone dibromide, 12.5 g. (0.092 mole) of sodium acetate, and 200 ml. of ethanol was refluxed for six hours. Addition of water and extraction with ether gave 15 g. (m.p. 153–156°); after repeated crystallizations from ethanol and isopropanol, m.p. 154–155°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10; N, 4.07.

Found: C, 59.36; H, 4.06; N, 4.10.

The dimorpholinyl ketone (see Table I) was obtained by the action of morpholine on

[13] This compound was erroneously reported to the Wiselogle Monograph (3) as the bromine-free compound (SN 4903).

either (a) the oil obtained by concentrating the ether extract (above), or (b) the isolated α-bromochalcone.

α-Bromo-β-morpholinyl-β-(4-methoxyphenyl)propiophenone, (*p*)$CH_3OC_6H_4CH(NC_4H_8O)$-$CHBrCOC_6H_5$, was isolated in an unsuccessful attempt to prepare the corresponding α,β-dimorpholinyl ketone. The structure is suggested on the basis of analogy (7).

A solution of 15 g. of 4-methoxychalcone dibromide (23), 200 ml. of ethanol, and 19.6 g. (6 equivalents) of morpholine was allowed to stand at room temperature for twenty-four hours, concentrated to one-third its volume and cooled; the resulting oil solidified slowly and was washed with ether and with water; 13 g., m.p. 72.5–74°; after six crystallizations from ethanol, m.p. 73.5–74°.

Anal. Calc'd for $C_{20}H_{22}BrNO_3$: C, 59.42; H, 5.49.

Found: C, 59.60; H, 5.88.

A second run (under reflux for four hours) gave 1.7 equivalents of morpholine hydrobromide but otherwise only resinous products.

α,β-Dimorpholinyl- and dipiperidyl-β-phenylpropiophenones (*cf.* III) (4, 6b, 7) were prepared by slowly adding five equivalents of the amine to a cooled suspension of chalcone dibromide in acetone, and allowing the mixtures to stand overnight (*cf.* Procedure C above).

NUCLEAR-SUBSTITUTED BENZALACETOPHENONES (CHALCONES)

Procedure A. 3',4'-Dichlorochalcone. Sodium hydroxide (100 ml.; 20%) was added slowly under stirring to a mixture of 65 g. (0.344 mole) of 3,4-dichloroacetophenone (24), 37 g. (0.349 mole) of benzaldehyde, and 300 ml. of ethanol, at a maintained temperature of 15–30°. Within one hour the mixture thickened and stirring became ineffective. After standing for ten hours at 2–5°, the pale yellow product was filtered, washed free of alkali with water, and finally was washed with 40 ml. of cold ethanol; 81 g. (85%); m.p. 110–112°. Three recrystallizations, once from benzene and twice from absolute ethanol, gave a pure product.

Procedure B. 2',5'-Dimethylchalcone. To a cooled mixture of 60 g. (0.41 mole) of 2,5-dimethylacetophenone, 80 ml. of 20% sodium hydroxide, and 275 ml. of ethanol, was added 42.9 g. (0.41) mole) of benzaldehyde under stirring and at such a rate that the reaction temperature did not exceed 27°. Stirring was continued for 2.5 hours. The oil was separated, washed, and fractionated; b.p. 203–204°/1 mm.; n_D^{25} 1.6300; 75 g. (77%).

Procedure C. 4'-Acetamido-4-dimethylaminochalcone. A mixture of 35.4 g. (0.2 mole) of 4-acetamidoacetophenone, 30 g. (0.2 mole) of 4-dimethylaminobenzaldehyde, 100 ml. of 20% sodium hydroxide, and 500 ml. of methanol at 30–45° was stirred for thirty minutes or until solution occurred. After cooling and standing overnight the orange precipitate was washed free of alkali, and dried; 33 g. (54%) m.p. 194–197°. Recrystallization from acetone-methanol yielded 20 g. of yellow rectangular prisms.

Procedure D. 4'-Carbethoxyamino-4-dimethylaminochalcone (*ethyl 4[(p-dimethylaminocinnamoyl)phenyl]carbanilate*). A solution of 11 g. of sodium in 200 ml. of methanol was added to a stirred mixture of 82 g. (0.4 mole) of purified ethyl 4-acetylcarbanilate, 60 g. (0.4 mole) of freshly recrystallized 4-dimethylaminobenzaldehyde, and 800 ml. of methanol. Upon refluxing for ten minutes a red solution resulted, and during two hours of refluxing an orange solid separated. Filtering while still warm, washing with water and with methanol, gave 84 g. (67%); m.p. 187–189°. Recrystallization from 1 liter of butanone gave a pure product; orange colored, 62 g., m.p. 188–189°.

This reaction when carried out at 40–45° for one hour, was incomplete. At first it was suspected that at higher temperatures cleavage of the ethyl carbanilate system occurred with possible formation of a Schiff base such as is described below (E).

Procedure E. 4-Dimethylamino-4'-(4-dimethylaminobenzylidineamino)chalcone [(*p*)$(CH_3)_2$-$NC_6H_4CH{=}CHCOC_6H_4N{=}CHC_6H_4N(CH_3)_2(p)$]. The synthesis was patterned after that of 4'-benzylidineaminochalcone (25).

Sodium hydroxide (100 ml.; 10%) was added to a stirred suspension of 13.5 g. of 4-aminoacetophenone and 30 g. of 4-dimethylaminobenzaldehyde in 200 ml. of methanol (38–40° for ten minutes); cooling and filtering gave 18 g. of orange-colored solid; m.p. 164–168°. Recrystallizations were from a butanone-ethanol mixture and from pyridine.

(4-Acetylphenyl)urea (26) was prepared in a new way by adding 100 g. of aluminum chloride under stirring and cooling to a mixture of 40 g. of phenylurea, 500 ml. of carbon disulfide, and 35 g. of acetyl chloride (15–20° for four hours); it was recrystallized from hot water; 16 g. (31%).

Ethyl 4-acetylcarbanilate (26) was prepared by a somewhat modified procedure, as follows: 32.4 g. of ethyl chloroformate was added to a stirred suspension of 40.5 g. of 4-aminoacetophenone in 800 ml. of ether followed by a solution of 12 g. of sodium hydroxide in 100 ml. of water. As the temperature rose from 20° to 30° a precipitate appeared. After cooling for thirty minutes and allowing to stand overnight at room temperature with consequent evaporation of solvent, 54 g. (70%) was obtained, m.p. 155–157°; recrystallized from benzene, m.p. 158–159°.

3-(4-Dimethylaminophenyl)-1-phenyl-2-propen-1-ol [(*p*)$(CH_3)_2NC_6H_4CH{=}CHCHOHC_6H_5$]. A mixture of 25.1 g. (0.1 mole) of 4-dimethylaminochalcone (27) and 200 ml. of 1.5 *N* aluminum isopropoxide was heated for three hours under partial reflux with distillation of most of the solvent. Hydrolysis with dilute sodium hydroxide, extraction with ether, concentration, and crystallization from *n*-heptane gave 9 g. (36%); m.p. 92–95°; two additional crystallizations and one more from isopropanol gave slightly yellow plates; m.p. 99–100°.

Anal. Calc'd for $C_{17}H_{19}NO$: C, 80.59; H, 7.56.

Found: C, 80.60; H, 7.58.

This compound, like other styrylmethanols (28), forms intensely colored solutions in dilute hydrochloric acid, but no crystalline product could then be recovered.

Nuclear-substituted benzalacetophenone (chalcone) dibromides. The new chalcone dibromides used in the synthesis of the dimorpholinyl ketones (listed in Table III) were made by dropwise addition of the calculated amount of bromine to a stirred solution of the chalcone in chloroform or carbon tetrachloride as solvent. Cooling, or evaporation in the case of the more soluble compounds, gave the dibromides in good yields.

THE COMPOUNDS MADE FROM BENZALPINACOLONE

1-tert.-Butyl-2,3-dimorpholinyl-3-phenyl-1-propanone (VI). Benzalpinacolone (29) was brominated in chloroform; yield 91%, m.p. 124–125°. A suspension of 44.8 g. of the *dibromide* in 150 ml. of ethanol was treated with 43.6 g. of morpholine (two hours under stirring); the resulting crystalline precipitate was filtered and washed with water; 17.7 g. (38.5%); m.p. 190.5–191.5°. It crystallized as pale yellow needles from ethanol; m.p. 194°.

Anal. Calc'd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95.

Found: C, 69.93; H, 9.04.

THE (4-HALOGENOBENZAL)ACETONE SERIES

(4-Chlorobenzal)acetone (30). Attempts to make this compound by the directions of Walther and Raetze (30), or by the standard procedure for benzalacetone (31), were unsuccessful. The following scheme was developed. A solution of 0.3 g. of sodium hydroxide in 170 ml. of ethanol, 40 ml. of acetone, and 230 ml. of water, was added dropwise to a solution of 10 g. of *p*-chlorobenzaldehyde in 60 ml. of ethanol over one hour under stirring. Yellow crystals began separating. After twelve hours of continued stirring, the solid was filtered; 3.5 g. (32%); m.p. 150–180°. Recrystallization from benzene gave pure bis-(4-chlorobenzal)-acetone; m.p. 193–194°;

Anal. Calc'd for $C_{17}H_{12}Cl_2O$: C, 67.34; H, 3.99.

Found: C, 67.27; H, 4.10.

The filtrate from the above, upon concentrating and diluting with water, gave 8.2 g. (64%) of product (m.p. 50–54°). Crystallization from ligroin gave needles, m.p. 59–59.5° [W. and R. (30) reported 50–51°].

Anal. Calc'd for $C_{10}H_9ClO$: C, 66.49; H, 5.02.

Found: C, 66.17; H, 5.10.

4-(4-Chlorophenyl)-3,4-dimorpholinylbutanone-2 (VIIb) (SN 8335). The dibromide of 4-(chlorobenzal)acetone [$ClC_6H_4CHBrCHBrCOCH_3$] was prepared by bromination in

carbon tetrachloride at room temperature (standing for nine hours), evaporation of the solvent, and crystallization from ligroin (yield 50%; m.p. 78–79.5°). A solution of 14 g. of the dibromide in 65 ml. of absolute ethanol was treated with 14.4 g. of morpholine. After fifteen minutes the precipitated morpholine hydrobromide was filtered (92%) and the filtrate on concentration gave a solid which was washed with, and then crystallized from, methanol; yield 6.3 g. (46%); m.p. 128.5–129°.

Anal. Calc'd for $C_{18}H_{25}ClN_2O_3$: N, 7.94.

Found: N, 7.71.

1-(4-Chlorophenyl)-5-(N,N-benzylmethylamino)-1-penten-3-one hydrobromide (XVI). A mixture of 5 g. of paraformaldehyde, 33 g. of benzylmethylamine hydrobromide, two drops of conc'd hydrobromic acid, 125 ml. of dry benzene, and 29.5 g. of 4-chlorobenzalacetone was refluxed for two hours and allowed to stand overnight (the calculated amount of water which was evolved was collected with a calibrated trap under the reflux condenser). Cooling gave 56.7 g.; recrystallization from absolute ethanol gave 37 g. (57%); m.p. 144–147°.

Anal. Calc'd for $C_{19}H_{20}ClNO \cdot HBr$: N, 3.55.

Found: N, 3.34.

1-(4-Chlorophenyl)-5-morpholinyl-1-penten-3-one hydrochloride, made as above, was precipitated by ether (yield 90%); recrystallized from 97% ethanol, m.p. 195–198°.

Anal. Calc'd for $C_{15}H_{18}ClNO_2 \cdot HCl$: Cl^-, 11.21.

Found: Cl^-, 11.46.

The *dibromide* of this [$ClC_6H_4CHBrCHBrCOCH_2CH_2NC_4H_8O \cdot HCl$] was made by dropwise addition of bromine to a cooled carbon tetrachloride solution of the above, over one hour. The crystalline precipitate was recrystallized from methanol; m.p. 156–157°.

Anal. Calc'd for $C_{15}H_{18}Br_2ClNO_2 \cdot HCl$: Cl^-, 7.45.

Found: Cl^-, 7.61.

Bis-(4-bromobenzal)acetone [$BrC_6H_4CH{=}CHCOCH{=}CHC_6H_4Br$]. The following procedure was designed to attain optimum yield of the mono-(4-bromobenzal) compound. A solution of 19.5 g. of *p*-bromobenzaldehyde in 112 ml. of ethanol was added over six hours under stirring to a solution of 0.6 g. of sodium hydroxide in 80.5 ml. of acetone, 340 ml. of ethanol, and 460 ml. of water. A yellow solid separated. After stirring for an additional six hours and acidification with conc'd acetic acid, the precipitate was filtered; 8 g. (39%). It was crystallized thrice from benzene; yellow, m.p. 211–211.5°.

Anal. Calc'd for $C_{17}H_{12}Br_2O$: Br, 40.76.

Found: Br, 40.77.

(4-Bromobenzal)acetone [$BrC_6H_4CH{=}CHCOCH_3$]. The filtrate from the crude bis-(4-bromobenzal) compound (above) was concentrated under reduced pressure and diluted with water. The precipitate (12.5 g.; 37%) was crystallized from ligroin (charcoal); m.p. 83–84°.

Anal. Calc'd for $C_{10}H_9BrO$: C, 53.35; H, 4.03.

Found: C, 53.48; H, 4.15.

The *dibromide* [$BrC_6H_4CHBrCHBrCOCH_3$] was made by dropwise addition of bromine in carbon tetrachloride to the 4-bromobenzal compound in this solvent. The yield of nearly pure product after crystallization from ligroin, was 65%. Further purification by recrystallization (charcoal) gave m.p. 104–104.5°.

Anal. Calc'd for $C_{10}H_9Br_3O$: C, 31.20; H, 2.36.

Found: C, 31.11; H, 2.40.

5-Morpholinyl-1-phenyl-1-penten-3-one hydrobromide was made in the usual way by the Mannich reaction from benzalacetone (in absolute ethanol, refluxing for five hours); recrystallized from absolute ethanol, m.p. 180–181°.

Anal. Calc'd for $C_{15}H_{19}NO_2 \cdot HBr$: N, 4.29. Found: N, 4.07.

4-(4-Bromophenyl)-3,4-dimorpholinyl-2-butanone (VIIc). A mixture of 15 g. of the dibromide (above), 75 ml. of absolute ethanol, and 15 g. of morpholine, after standing for twenty-four hours, was filtered to remove morpholine hydrobromide (11.8 g.) and evaporated. The residue, which solidified, was washed with and recrystallized from methanol; 3.2 g., m.p. 169–170°.

Anal. Calc'd for $C_{18}H_{25}BrN_2O_3$: N, 7.05. Found: N, 6.80.

1-(4-Bromophenyl)-5-(N,N-benzylmethylamino)-1-penten-3-one hydrobromide (XVI) was made like the 4-chloro analog, but under three hours of refluxing. The product was precipitated by addition of dry ether and recrystallized from absolute ethanol, yield 44%; crystallized thrice from absolute ethanol, m.p. 154–155°.

Anal. Calc'd for $C_{19}H_{20}BrNO \cdot HBr$: N, 3.15. Found: N, 3.09.

THE 4-CHLORO- AND 4-BROMO-α,β-DIMORPHOLINYLPROPIOPHENONES

α,β-Dibromo-4-chloropropiophenone (IX). A solution of 50 g. (0.2 mole) of α,β-dibromopropionyl chloride (VIII) in 30 ml. of carbon disulfide was added over one hour to a stirred mixture of 22.5 g. (0.2 mole) of chlorobenzene, 33.4 g. (0.25 mole) of anhydrous aluminum chloride, and 100 ml. of carbon disulfide, and the mixture was refluxed for 15 min. Hydrolysis with ice and hydrochloric acid, extraction with ether, washing, and evaporation gave a solid residue which was crystallized from ethanol; 55.5 g. (85%); m.p. 56–57°. Recrystallization thrice from ethanol gave m.p. 57–58°.

Anal. Calc'd for $C_9H_7Br_2ClO$: C, 33.11; H, 2.16.
Found: C, 33.42; H, 2.50.

4-Chloro-α,β-dimorpholinylpropiophenone (Xa). Morpholine (45 g.) was added slowly over thirty minutes to a cooled solution of 30 g. of XVII in 100 ml. of acetone. The mixture, after refluxing for one hour and standing at room temperature for four hours, was filtered and evaporated. The residual oil was washed; it ultimately crystallized, and washing with petroleum ether gave 3.8 g. (76%). It was recrystallized twice from ethanol (charcoal), m.p. 96–97°.

Anal. Calc'd for $C_{17}H_{23}ClN_2O_3$: N, 8.27. Found: N, 8.05.

4-Chloro-α,β-bis-(2-methyl-4-morpholinyl)propiophenone was prepared like Xa (above) except that absolute ether was used as the solvent, and crystallizations were from butanone; m.p. 154–155°. The 2-methylmorpholine (11) was furnished by Dr. W. S. Cottle.

Anal. Calc'd for $C_{19}H_{27}ClN_2O_3$: N, 7.64. Found: N, 7.86.

α,β,4-Tribromopropiophenone (13) was prepared by adding 60 g. (0.24 mole) of VIII over one hour to 36 g. (0.24 mole) of bromobenzene and 35 g. of anhydrous aluminum chloride in 400 ml. of carbon disulfide at 5°, and allowing the mixture to stand for twelve hours at room temperature. Crystallization of the product from ethanol gave 70 g. (78%). Three crystallizations from ethanol (once with charcoal) gave a pure sample; m.p. 56–57°. Kohler's product (13) obtained under different reaction conditions melted at 74° and may be either a stereoisomer or a different crystalline form.

Anal. Calc'd for $C_9H_7Br_3O$: C, 29.14; H, 1.90.
Found: C, 29.32; H, 2.00.

4-Bromo-α,β-dimorpholinylpropiophenone (Xb) (SN 6551). A solution of 30 g. of XVII in 150 ml. of absolute ether at 0° was treated with 29 g. of morpholine, and was filtered after three hours standing. Evaporation, washing, and crystallization from methanol gave 22.5 g. (73%). Three crystallizations from methanol, once with charcoal, gave m.p. 101.5–102°.

Anal. Calc'd for $C_{17}H_{23}BrN_2O_3$: C, 53.28; H, 6.05.
Found: C, 53.50; H, 6.15.

α,β-DIMORPHOLINYL KETONES CONTAINING A NAPHTHALENE RING

α,β-Dimorpholinyl-β-phenyl-1-propionaphthone (XI). Benzaldehyde (37 g.; 0.35 mole) was added fairly rapidly to a stirred mixture of 59.8 g. (0.35 mole) of methyl 1-naphthyl ketone, 18 g. of sodium hydroxide, 100 ml. of ethanol, and 160 ml. of water (cooled during the addition), and stirring was continued for eighteen hours. The yellow oil, *benzal-1-acetonaphthone* (not analyzed) was extracted with ether and this solution was treated dropwise with 56 g. (0.35 mole) of bromine with short heating initially to start the reaction. After stirring for two hours the solid *dibromide* was filtered; 118 g. (81%); m.p. 165–171° (not analyzed). A suspension of 17.7 g. of the dibromide in 100 ml. of absolute ethanol and 17.4 g. of morpholine was refluxed for thirty minutes, cooled and filtered, and the solid residue washed with water; yield 11.4 g. (66%); m.p. 185–189°. Recrystallization from ethyl acetate gave colorless needles; m.p. 202°.

Anal. Calc'd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02.
Found: C, 75.52; H, 7.36.

β-Phenyl-α,β-bis(1,2,3,4-tetrahydro-2-isoquinolyl)-1-propionaphthone was made similarly in 81% yield from the above dibromide in acetone medium (mixture shaken for fifteen minutes); crystallized from ethanol-chloroform mixture; light yellow needles; yield 26%; m.p. 176–177°.

Anal. Calc'd for $C_{37}H_{36}N_2O$: N, 5.34. Found: N, 5.15.

α-Morpholinyl-β-phenyl-1-acrylonaphthone (XIII). A suspension of 16.7 g. of the above dibromide in 100 ml. of absolute ethanol was treated with 20 ml. of methanol containing one equivalent (0.9 g.) of dissolved sodium, and was allowed to stand overnight. The resulting *mono-bromo* compound (not isolated) was treated with 3.9 g. of morpholine under cooling and the mixture was allowed to stand for 1½ hours at room temperature. The suspension of the solid *α-bromo-β-morpholinyl compound* (not characterized) was treated with a solution of 1.4 g. of sodium in 20 ml. of methanol (stirring for 15 min.). Cooling and filtering gave 10.5 g. (76%); recrystallized from ethanol, yellow, m.p. 116°.

Anal. Calc'd for $C_{23}H_{21}NO_2$: N, 4.08. Found: N, 4.22.

β-Phenyl-2-acrylonaphthone [$C_6H_5CH{=}CHCOC_{10}H_7(\beta)$]. A mixture of 59.8 g. of methyl 2-naphthyl ketone, 18 g. of sodium hydroxide, 150 ml. of ethanol, 100 ml. of water, and 37.1 g. (0.35 mole) of benzaldehyde, cooled initially, was allowed to stand for 45 min., and the precipitate (88.3 g.; 98%) was recrystallized from ethanol; diamond-shaped plates; m.p. 105°.

Anal. Calc'd for $C_{19}H_{14}O$: C, 88.34; H, 5.46.
Found: C, 88.41; H, 5.52.

The *dibromide* was made by dropwise addition of bromine to a cooled chloroform solution and subsequent addition of ether and cooling; the precipitate (61%) was recrystallized from ethyl acetate and ethanol; thick needles; m.p. 175°.

Anal. Calc'd for $C_{19}H_{14}Br_2O$: C, 54.58; H, 3.38.
Found: C, 54.92; H, 3.21.

α,β-Dimorpholinyl-β-phenyl-2-propionaphthone was prepared in 62% yield according to procedure A (above); it crystallized as needles from ethanol; m.p. 165.5–167°.

Anal. Calc'd for $C_{27}H_{30}N_2O_3$: C, 75.32; H, 7.02.
Found: C, 75.53; H, 6.80.

α,β-Dibromo-β-1-naphthylpropiophenone [$(\alpha)C_{10}H_7CHBrCHBrCOC_6H_5$]. α-Naphthaldehyde (31.2 g.) was added under stirring to a cooled mixture of 24 g. of acetophenone, 200 ml. of ethanol, and 100 ml. of 10% sodium hydroxide, cooled initially and allowed to stand at room temperature for two hours. The oil, *β-1-naphthylacrylophenone* (not characterized) was extracted with ether and brominated by dropwise addition of 28.8 g. of bromine. The precipitate, and a second crop obtained from concentration of the solution, was 53.7 g. (64%); it crystallized from ethyl acetate as square plates; m.p. 176°.

Anal. Calc'd for $C_{19}H_{14}Br_2O$: C, 53.58; H, 3.38.
Found: C, 54.69; H, 3.47.

α,β-Dimorpholinyl-β-1-naphthylpropiophenone (XII). The mixture obtained according to Procedure A (above) seemed, from the analysis, to consist of a mixture of the desired compound and the α-morpholinyl unsaturated ketone. No attempt was made to work up and to isolate the latter. The mixture was recrystallized from ethanol (by dilution with water) and from a 3:1 ethanol-ethyl acetate mixture; pale yellow needles; m.p. 161°.

Anal. Calc'd for $C_{27}H_{30}N_2O_3$: N, 6.51. Found: N, 6.67.

COMPOUNDS MADE FROM DIBENZALACETONE

5-Morpholinyl-1,5-diphenyl-1-penten-3-one (XV) was prepared by the action of 26 g. (0.3 mole) of morpholine in 250 ml. of dry ether on 23.4 g. (0.1 mole) of dibenzalacetone (8.5 hours). The resulting white precipitate was filtered; 28.5 g. (90%); m.p. 134–136°; recrystallized from ethyl acetate, m.p. 142.5–144°.

Anal. Calc'd for $C_{21}H_{23}NO_2$: N, 4.36. Found: N, 4.46.

When heated in 60% ethanol it was converted back into dibenzalacetone with loss of morpholine. Attempts to get the dimorpholine addition compound failed.

TABLE IV

ANALYSES

COMPOUND NO. (TABLES I-III)	CRYSTALLIZED FROM[a]	EMPIRICAL FORMULA	CARBON (OR NITROGEN = N)		HYDROGEN	
			Calc'd	Found	Calc'd	Found
1	Ethanol	$C_{24}H_{30}N_2O_3$	7.10	7.24	—	—
2	IsoPr.	$C_{26}H_{34}N_2O_3$	N6.63	6.32	—	—
3	Abs. EtOH	$C_{27}H_{36}N_2O_3$	N6.42	6.61	—	—
4	EtOH-EtOAc	$C_{29}H_{38}N_2O_3$	N6.06	6.04	—	—
5	Ethanol	$C_{31}H_{36}N_2O_3$	76.83	76.57	7.46	7.51
			N5.78	5.81	—	—
6	Acet. EtOH	$C_{29}H_{32}N_2O_3$	N6.14	6.10	—	—
7	Ligroin	$C_{23}H_{27}ClN_2O_3$	N6.75	7.08	—	—
8	Ethanol	$C_{23}H_{27}BrN_2O_3$	N6.10	5.78	—	—
9	Methanol	$C_{23}H_{27}N_3O_5$	64.92	65.05	6.40	6.55
			N9.88	9.92	—	—
10	Abs. EtOH	$C_{25}H_{31}N_3O_4$	68.31	68.02	7.14	6.97
			N9.60	9.69	—	—
11	Hept. tol.	$C_{26}H_{33}N_3O_5$	N8.99	9.02	—	—
12	Ethanol	$C_{24}H_{30}N_2O_4$	N6.83	6.62	—	—
13	Ethanol	$C_{25}H_{32}N_2O_4$	N6.60	6.75	—	—
14	Ethanol	$C_{26}H_{34}N_2O_4$	N6.39	6.48	—	—
15	Ethanol	$C_{26}H_{34}N_2O_4$	N6.39	6.34	—	—
16	Abs. EtOH	$C_{27}H_{36}N_2O_4$	71.65	71.41	7.84	8.35
			N6.19	6.10	—	—
17	Benz. ligr.	$C_{29}H_{32}N_2O_4$	N5.93	6.38	—	—
18	Methanol	$C_{26}H_{34}N_2O_4$	N6.39	6.68	—	—
19	Methanol	$C_{23}H_{27}ClN_2O_3$	N6.75	6.57	—	—
20	Ethanol	$C_{24}H_{30}N_2O_3$	73.07	73.25	7.67	8.08
21	Ethanol	$C_{23}H_{27}N_3O_5$	64.92	64.73	6.40	6.67
22	Ethanol	$C_{24}H_{30}N_2O_4$	70.22	69.93	7.37	7.51
23	Ethanol	$C_{25}H_{32}N_2O_3$	N6.86	6.76	—	—
24	Ethanol	$C_{29}H_{40}N_2O_3$	N6.03	5.85	—	—
25	Ethanol	$C_{23}H_{26}Cl_2N_2O_3$	N6.24	6.22	—	—
26	Ethanol	$C_{25}H_{31}BrN_2O_5$	57.81	58.42	6.02	6.10
			N5.39	5.08	—	—
27	Ethanol	$C_{25}H_{32}N_2O_5$	N6.36	6.12	—	—
28	Ethanol	$C_{24}H_{29}ClN_2O_3$	N6.53	6.71	—	—
29	Lig. EtOAc	$C_{27}H_{36}N_2O_4$	N6.19	6.04	—	—
30	Ethanol	$C_{26}H_{34}N_2O_3$	N6.63	6.88	—	—
31	Ethanol	$C_{27}H_{36}N_2O$	N6.93	7.12	—	—
32	Ethanol	$C_{27}H_{36}N_2O$	N6.93	7.24	—	—
33	Ethanol	$C_{26}H_{34}N_2O_2$	76.81	76.78	8.43	8.23
			N6.89	6.72	—	—
34	Ethanol	$C_{31}H_{36}N_2O_2$	N5.99	6.03	—	—
35	EtOH-$CHCl_3$	$C_{34}H_{34}N_2O_2$	N5.57	5.48	—	—
36	Methanol	$C_{29}H_{28}N_2O$	N6.66	6.95	—	—
37	Ethanol	$C_{27}H_{30}N_2O_2$	78.23	78.32	7.30	7.62
38	Methanol	$C_{30}H_{30}N_2O$	N6.45	6.53	—	—
39	Acetone	$C_{25}H_{26}N_2O_2$	N7.25	7.41	—	—
40	Methanol	$C_{26}H_{28}N_2O_2$	N7.00	7.06	—	—

TABLE IV—*Concluded*

COMPOUND NO. (TABLES I–III)	CRYSTALLIZED FROM[a]	EMPIRICAL FORMULA	CARBON (OR NITROGEN = N)		HYDROGEN	
			Calc'd	Found	Calc'd	Found
42	Hexane	$C_{25}H_{23}NO_2$	81.27	80.87	6.28	6.46
			N 3.79	3.84	—	—
43	Methanol	$C_{19}H_{18}ClNO_2$	N 4.27	4.06	—	—
44	Hexane	$C_{19}H_{18}BrNO_2$	61.30	61.04	4.87	4.67
			N 3.76	4.03	—	—
45	Heptane	$C_{19}H_{18}N_2O_4$	N 8.28	8.10	—	—
46	EtOAc-pet.	$C_{20}H_{21}NO$	82.43	82.27	7.26	7.48

CPD. NO.	EMPIRICAL FORMULA	ANALYSIS				CPD. NO.	ANALYSIS			
		C (or N)		H			C (or N)		H	
		Calc'd	Found	Calc'd	Found		Calc'd	Found	Calc'd	Found
49	$C_{21}H_{22}O$	86.85	86.65	7.64	7.48	68	52.96	52.95	4.46	4.55
50	$C_{23}H_{20}O$	88.42	87.81	6.45	6.33	69	53.80	53.92	4.75	4.79
51	$C_{17}H_{15}NO_2$	N 5.28	5.29	—	—	71	58.49	58.32	4.27	4.79
52	$C_{18}H_{17}NO_3$	N 4.74	4.74	—	—	72	56.78	57.05	3.63	3.73
53	$C_{16}H_{14}N_2O_2$	N 10.52	10.54	—	—	73	44.76	44.48	2.75	2.81
54	$C_{18}H_{18}O_2$	81.17	80.93	6.81	6.50	74	48.02	47.76	3.56	3.45
							N 3.30	3.28	—	—
55	$C_{18}H_{18}O_2$	81.17	81.41	6.81	7.07	75	47.50	47.71	3.76	3.66
57	$C_{19}H_{21}NO_2$	N 5.02	5.00	—	—	76	50.73	51.00	4.26	4.08
58	$C_{17}H_{16}O$	86.40	86.38	6.83	6.71	77	50.73	50.77	4.26	4.49
59	$C_{15}H_{10}Cl_2O$	64.77	64.95	3.64	3.79	78	51.84	51.44	4.58	4.53
60	$C_{16}H_{13}ClO$	74.85	74.62	5.10	4.96	79	50.30	50.32	3.69	3.80
61	$C_{19}H_{20}O_2$	81.40	81.64	7.19	7.51	80	48.27	48.41	3.54	3.19
62	$C_{19}H_{20}N_2O_2$	N 9.09	9.48	—	—	81	51.41	51.72	4.06	3.96
63	$C_{21}H_{24}N_2O_2$	N 8.33	8.52	—	—	82	55.77	55.62	5.35	5.36
64	$C_{20}H_{22}N_2O_3$	N 8.28	8.56	—	—	83	41.22	41.12	2.31	2.69
65	$C_{22}H_{26}N_2O_3$	72.10	71.56	7.15	7.12	84	47.27	46.12	3.22	3.31
		N 7.65	7.83	—	—					
66	$C_{18}H_{19}N_3O_2$	N 13.58	13.83	—	—	85	51.84	51.68	4.58	4.69
67	$C_{26}H_{27}N_3O$	78.55	78.52	6.85	6.97	86	47.69	47.24	3.77	3.55

[a] Solvent abbreviations: isoPr. = isopropanol; EtOAc = ethyl acetate; acet. = acetone; hept. = heptane; tol. = toluene; benz. = benzene; ligr. = ligroin; pet. = petroleum ether.

1,5-Diphenyl-5-piperidyl-1-penten-3-one was prepared similarly by the action of piperidine on dibenzalacetone in ligroin (12 hours), yield 78%; repeated recrystallizations from ligroin gave m.p. 91–92°.

Anal. Calc'd for $C_{22}H_{25}NO$: N, 4.39. Found: N, 4.30.

Attempts to obtain the dipiperidyl addition compound indicated that it was formed to some extent but was unstable, and it was not isolated pure.

Attempts to add dibutylamine to dibenzalacetone failed.

Catalytic reduction of dibenzalacetone (32) to dibenzylacetone was accomplished effectively by means of Raney nickel in 95% ethanol at atmospheric pressure (three hours).

2,4-Dibromo-1,5-diphenylpentan-3-one. Dibromination of dibenzylacetone (above) was effected in absolute ether. The reaction mixture was cooled after initiating the reaction with

a few drops of bromine. After washing the solution with water and evaporating, the residue was fractionally crystallized from ligroin. The first fraction (55%) was *isomer-A;* m.p. 96–99°; recrystallization from ligroin gave m.p. 100.5–101°.

Anal. Calc'd for $C_{17}H_{16}Br_2O$: Br, 40.25. Found: Br, 40.92.

The second crop was a mixture of isomers. The filtrate on evaporation gave a 6% yield of material of m.p. 63.5–65°, *isomer-B,* which after repeated crystallizations from isopropanol had m.p. 64.5–65°.

Anal. Calc'd for $C_{17}H_{16}Br_2O$: Br, 40.25. Found: Br, 39.98.

2,4-Dimorpholinyl-1,5-diphenylpentan-3-one (XIV) was made by adding morpholine dropwise to an ether solution of either of the isomeric dibromo ketones (above) and allowing the mixture to stand overnight at room temperature. A 56% yield was obtained in the case of *isomer-A* by crystallization of the products from isopropanol; m.p. 120–121°.

Anal. Calc'd for $C_{25}H_{32}N_2O_3$: N, 6.86. Found: N, 6.41.

SUMMARY

α,β-Dimorpholinyl-β-phenylpropiophenone was found to be one-tenth as active as quinine against avian malaria. Derivatives have been made with various nuclear substituents, including alkyl, phenyl, halogen, alkoxyl, nitro, acetamido, and carbethoxyamino, and many of these show similar antimalarial activity. The synthesis of these compounds has involved the preparation of a number of new chalcones and their dibromides, and some related α-morpholinyl chalcones. Absorption spectra of six of the substituted chalcones are reported.

New preparations of β-morpholinyl and β-piperidyl chalcones are described.

α,β-Dimorpholinyl ketones were made from the following: benzalpinacolone, *p*-chloro- and *p*-bromo-benzalacetones, *p*-chloro- and *p*-bromo-phenyl vinyl ketones, benzal-1 (and -2) -acetonaphthones, and α-naphthalacetophenone.

α,α′-Dimorpholinyldibenzylacetone is described. Attempts to make the β,β′-analog from dibenzalacetone gave only the mono-morpholine addition product.

Some new Mannich reaction products from *p*-chloro- and *p*-bromo-benzalacetone are described.

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REFERENCES

(1) AMACKER, Doctorate Dissertation, University of Virginia (1943).
(2) SHEARER, M. S. Thesis, University of Virginia (1944).
(3) WISELOGLE, *"A Survey of Antimalarial Drugs,"* 1941–1945, J. W. Edwards (1946).
(4) (a) DUFRAISE AND MOUREU, *Bull. soc. chim.,* **41,** 457, 850 (1927); (b) CROMWELL, *J. Am. Chem. Soc.,* **62,** 1672 (1940); (c) CROMWELL, *J. Am. Chem. Soc.,* **62,** 2897 (1940).
(5) LUTZ AND SMITH, results to be published shortly.
(6) WATSON, *J. Chem. Soc.,* **85,** 1319 (1904).
(7) (a) CROMWELL, *Chem. Revs.,* **38,** 83 (1946); (b) CROMWELL, Abstr. of Papers, Atlantic City Meeting of the American Chemical Society, page 28k, April (1946).
(8) FERNOLD AND GEIGER, Abstr. of Papers, Atlantic City Meeting of the American Chemical Society, p. 13B, April (1947).
(9) (a) ALEXA, *Bul. soc. chim. România,* **18A,** 67, 83, 93 (1936); (b) CROMWELL AND JOHNSON, *J. Am. Chem. Soc.,* **65,** 316 (1943).
(10) DUFRAISE AND NETTER, *Bull. soc. chim.,* **51,** 550 (1932).

(11) COTTLE, JELTSCH, STOUDT, AND WALTERS, *J. Org. Chem.*, **11,** 286 (1946).
(12) DAVIS, *J. Am. Chem. Soc.*, **63,** 1667 (1941).
(13) KOHLER, *Am. Chem. J.*, **42,** 375 (1909).
(14) RAIFORD AND DAVIS, *J. Am. Chem. Soc.*, **50,** 158 (1928).
(15) WEYGAND, MENSDORF, AND STROBELT, *Ber.*, **68,** 1825 (1935).
(16) GIUA AND BAGIELLAE, *Gazz. chim. ital.*, **51,** 116 (1921).
(17) GIUA, *Gazz. chim. ital.*, **46,** 289 (1916).
(18) CROMWELL AND WITT, *J. Am. Chem. Soc.*, **65,** 308 (1943).
(19) *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 205 (1941).
(20) POND, YORK, AND MOORE, *J. Am. Chem. Soc.*, **23,** 792 (1901).
(21) ANDRÉ, *Ann. chim. et phys.*, **29,** 540 (1913).
(22) ANWERS AND RISSE, *Ber.*, **64,** 2216 (1931).
(23) POND AND SCHOFFSTALL, *J. Am. Chem. Soc.*, **22,** 656 (1900).
(24) ROBERTS AND TURNER, *J. Chem. Soc.*, 1855 (1927).
(25) SCHOLTZ AND HUBER, *Ber.*, **37,** 390 (1904).
(26) RAADSVELD, *Rec. trav. chim.*, **54,** 813 (1935); **54,** 827 (1935).
(27) SACHS AND LEWIN, *Ber.*, **35,** 3569 (1902).
(28) LUND, *Ber.*, **70,** 1520 (1937).
(29) HILL AND BRAMANN, *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 81 (1941).
(30) WALTHER AND RAETGE, *J. prakt. Chem.*, **65,** 280 (1902).
(31) GILMAN AND BLATT, *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 77 (1941).
(32) WEIDLICH AND MEYER-DELINS, *Ber.*, **74,** 1195 (1941).