Table II. Percentage Composition of Possible $CuCl_2$–Dioxane Compounds

Compound	% $CuCl_2$	C	H	O
$CuCl_2 \cdot C_4H_8O_2$	60.41	21.59	3.62	14.37
$CuCl_2 \cdot 2(C_4H_8O_2)$	43.28	30.93	5.19	20.60
$2(CuCl_2) \cdot C_4H_8O_2$	75.32	13.46	2.26	8.96
$3(CuCl_2) \cdot 2(C_4H_8O_2)$	69.60	16.58	2.78	11.04
Sample 1 (dull orange)[a]	69.77	16.56	2.82	11.27
Sample 2 (reddish orange)[a]	69.56	16.25	2.70	11.27

[a] Analyses for the reaction product isolated in this work (see discussion).

the average $CuCl_2$ percentage was 69.56 ± 0.10. A mixture of dioxane and $CuCl_2$ that was allowed to stand for several months produced the dull orange solid described above. This solid contained 69.43% $CuCl_2$. Table II shows the results of a carbon-hydrogen-oxygen analysis (Schwarzkopf Laboratories) on samples of the dried solid.

The compound $3(CuCl_2) \cdot 2(C_4H_8O_2)$, insoluble in dioxane, is stable in dry air, but absorbs water readily (and turns green on the surface) from moist air.

The color of the saturated liquid phase varied from a dark green near the methanol–$CuCl_2$ axis to a lighter green near the dioxane apex. The absorption spectrum of $CuCl_2$ in the solution is dependent upon the percentage dioxane in the mixture. For the system dioxane–isopropyl alcohol–$CuCl_2$, (saturated $CuCl_2$) solutions high in dioxane content are orange-red, while those high in isopropyl alcohol content are dark green. The same dark green was observed in the high methanol solutions studied in this paper, but the spectral shift as the per cent dioxane increased was not so marked. No color was observed in the liquid phase for $CuCl_2$–dioxane mixtures.

A previous study (*1*) has shown the existence of $CuCl_2 \cdot CH_3OH$. Therefore, samples were prepared with compositions (1% dioxane or less) near the CH_3OH–$CuCl_2$ axis in order to locate the $CuCl_2 \cdot CH_3OH$–$3(CuCl_2) \cdot 2(C_4H_8O_2)$–saturated solution invariant point. These mixtures were made by adding a few drops of dioxane to a saturated solution of $CuCl_2$ in methanol in equilibrium with the green $CuCl_2$–CH_3OH. The resultant solid phase appeared to be a mixture of the green solid and the reddish solid that appeared immediately upon addition of the dioxane. Addition of more than several drops of dioxane led to the disappearance of the green solid and to a sharp reduction (see Figure 1) in the $CuCl_2$ concentration in the liquid phase.

The analyses of the saturated liquids from these samples yielded $CuCl_2$ percentages from 37.61 to 37.74 (note first row of Table I). The refractive indices of the distillates from the saturated liquids corresponded to dioxane contents of the liquid phase between 0 and 0.4%. These results indicate that the per cent dioxane in the invariant liquid is less than 0.4, and that $CuCl_2 \cdot CH_3OH$ is unstable in the presence of even trace amounts of dioxane.

ACKNOWLEDGMENT

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Some Novel Ketones and Quinolines

Intermediates 2,4,6-Tris(*m*-trifluoromethylphenyl)-*s*-triazine, Bis(*m*-trifluoromethyl)dibenzamide, and Tris(*m*-trifluoromethyl)tribenzamide

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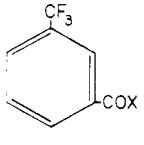
SOME ANALOGS of acetophenone (I), such as *m*-trifluoromethylpropiophenone (II), *m*-trifluoromethylbutyrophenone (III), *m*-trifluoromethylvalerophenone (IV), and 3′-trifluoromethyl-2-phenylacetophenone (V), have been prepared as intermediates in the synthesis of a number of trifluoromethyl derivatives of quinoline, which are expected to produce interesting pharmacological effects. These ketones were obtained by a process similar to that used for *m*-trifluoromethylphenylacetophenone (*2*), by interaction of *m*-trifluoromethylbenzonitrile (*5*) and the appropriate organomagnesium halide. The preparation of III, IV, and V led to a common byproduct which was obtained in maximum yield from interaction of *m*-trifluoromethylbenzonitrile and benzylmagnesium bromide, and was shown to be

m-Trifluoromethylpropiophenone, m-trifluoromethylbutyrophenone, m-trifluoromethylvalerophenone, and 3'-trifluoromethyl-2-phenylacetophenone have been synthesized. During preparation of the last three ketones, 2,4,6-(m-trifluoromethylphenyl)-s-triazine was obtained as a common byproduct. To confirm the identity of this compound, it was also prepared by interaction of chlorosulfonic acid and m-trifluoromethylbenzonitrile; bis(m-trifluoromethyl)dibenzamide, which could be converted into tris(m-trifluoromethyl)tribenzamide, was obtained simultaneously with the triazine derivative. 2-(3'-Trifluoromethylphenyl)quinoline, 2-(3'-trifluoromethylphenyl)-3-methylquinoline, 2-(3'-trifluoromethylphenyl)-3-ethylquinoline, and 2-(3'-trifluoromethylphenyl)-3-phenylquinoline were also obtained. The 4-carboxy, 6-bromo, and 6-bromo-4-carboxy derivatives of these quinolines were also prepared.

the hitherto unreported 2,4,6-tris(*m*-trifluoromethylphenyl)-*s*-triazine (VI). For purposes of identification, it was also prepared by two other processes: boiling *m*-trifluoromethylbenzonitrile with sodium in benzene, and interaction of chlorosulfonic acid and *m*-trifluoromethylbenzonitrile in the cold. In the latter process, in addition to 2,4,6-tris(*m*-trifluoromethylphenyl)-*s*-triazine, another new compound, bis(*m*-trifluoromethyl)dibenzamide (VII), was obtained in good yield, whereas the interaction of benzonitrile and chlorosulfonic acid gave only 2,4,6-triphenyl-*s*-triazine (cyaphenine) without the dibenzamide. Here, the presence of a CF_3 group in the meta- position must be responsible for this special behavior of *m*-trifluorobenzonitrile resulting in the formation of VII. The reaction of VII with *m*-trifluoromethylbenzoyl chloride in pyridine, gave tris(*m*-trifluoromethyl)tribenzamide (VIII).

To prepare the allyl derivatives of the above ketones, the preparation of allyl phenyl ketone was attempted, but the reaction of vinylacetyl chloride (*3*) and benzene in the presence of anhydrous aluminum trichloride gave β-phenylbutyrophenone (*1*), quantitatively, instead of α-vinylacetophenone. Although this ketone contains an α-methylenecarbonyl group, it could not be made to undergo the Pfitzinger reaction, even under extreme conditions, nor did it give a benzylidene. Steric hindrance may be responsible for the exceptional behavior of this α-methylenecarbonyl compound.

All of the above ketones possessing trifluoromethyl groups gave, in reaction with isatin or 5-bromoisatin in alcoholic potassium hydroxide (*4*), the corresponding quinolinecarboxylic acids, which, after decarboxylation, were converted into the corresponding quinolines (Table II).



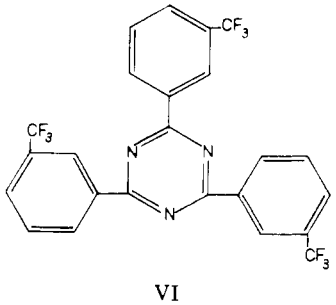
I $X = CH_3$

II $X = C_2H_5$

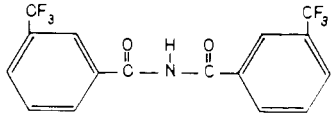
III $X = n\text{-}C_3H_7$

IV $X = n\text{-}C_4H_9$

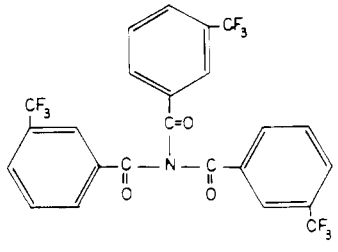
V $X = CH_2C_6H_5$



VI



VII



VIII

EXPERIMENTAL

Preparation of Ketones. In all cases, 0.11 mole of organomagnesium halide was prepared and added drop by drop, with stirring, to an ethereal solution of 0.1 mole of *m*-trifluoromethylbenzonitrile. The mixtures were stirred for 3 hours at room temperature, decomposed with ice and HCl, extracted with ether, and after removal of ether, the ketones were distilled. The ketones obtained are listed in Table I.

2,4,6 - Tris (*m* - trifluoromethylphenyl) -*s*- triazine (VI). A. DURING THE PREPARATION OF KETONES. During the distillation of III, IV, and V, some solid product was formed in the condenser and the distillate, and a considerable amount of the same solid remained in the distillation flask. This product, which was sparingly soluble in methanol and ethanol, soluble in benzene and petroleum ether, had a m.p. of 208° C. after four crystallizations in benzene. The infrared spectrum of the product showed neither carbonyl nor nitrile group absorptions. Anal. Calcd. for $C_{24}H_{12}F_9N_3$: C, 56.14; H, 2.33; F, 33.33; N, 8.18. Found: C, 56.30; H, 2.37; F, 32.99; N, 8.27.

B. PREPARATION OF VI FROM SODIUM AND *m*-TRIFLUOROMETHYLBENZONITRILE IN BOILING BENZENE. A mixture of 50 ml. of anhydrous benzene, 13.5 grams of *m*-trifluoromethylbenzonitrile, and 2 grams of fine sodium wire was refluxed for 10 hours and filtered through a fluted filter paper to remove the excess sodium. The filtrate was washed with water, dried, and evaporated. The residue after crystallization in benzene gave 0.65 gram of product, m.p. 208° C. This product mixed with the product obtained in A had a m.p. of 208° C., and the infrared spectra of the products obtained in A and B were identical.

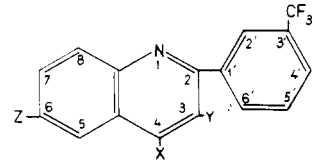
C. FROM CHLOROSULFONIC ACID AND *m*-TRIFLUOROMETHYLBENZONITRILE. To 130 ml. of chlorosulfonic acid, cooled to 0° in a cooling bath containing ice-salt mixture, 15 grams of *m*-trifluoromethylbenzonitrile were added drop by drop. The mixture was kept in a refrigerator for 48 hours, poured on ice, and washed several times with iced water. The residue, dried and crystallized from toluene, gave 10 grams of a solid material. When boiled in methanol, part of this solid material dissolved. The insoluble portion was dissolved in benzene and, when crystallized, gave 4.5

Table I. Ketones

X	B.P., °C.	Pressure, Mm. Hg	Yield, %	Formula	Analyses[a] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I CH_3[b]	198–9	(760)	79	$C_9H_7F_3O$	57.44	57.60	3.72	3.70
II C_2H_5[c]	123–5	(5)	70	$C_{10}H_9F_3O$	59.40	59.18	4.45	4.51
III n-C_3H_7[d]	138–40	(20)	65	$C_{11}H_{11}F_3O$	61.11	61.20	5.09	5.12
IV n-C_4H_9[e]	126–8	(5)	65	$C_{12}H_{13}F_3O$	62.60	62.51	5.65	5.61
V CH_2-C_6H_5[f]	166–8	(5.5)	76	$C_{15}H_{11}F_3O$	68.18	68.19	4.16	4.19

[a] Analyses were performed by F. Pascher, Mikroanalytiches Laboratorium, Bonn, W. Germany. [b] Semicarbazone, m.p. 205–6° C. [c] Semicarbazone, m.p. 166° C. [d] Semicarbazone, m.p. 126° C.; dinitrophenylhydrazone, m.p. 114° C. [e] $n^{27}D$ 1.4639; semicarbazone, m.p. 131° C.; dinitrophenylhydrazone, m.p. 115° C. [f] $n^{26}D$ 1.5327; benzylidene, m.p. 156° C.; semicarbazone, m.p. 160° C.; dinitrophenylhydrazone, m.p. 166° C.

Table II. Quinolines and Quinolinecarboxylic Acids



X	Y	Z	M.P., °C.	Picrate, M.P., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
COOH	H	H	185	...	$C_{17}H_{10}F_3NO_2$	4.41	4.50
COOH	H	Br	230	...	$C_{17}H_9BrF_3NO_2$	3.53	3.52
COOH	CH_3	H	266	...	$C_{18}H_{12}F_3NO_2$	4.22	4.18
COOH	CH_3	Br	295	...	$C_{18}H_{11}BrF_3NO_2$	3.41	3.38
COOH	C_2H_5	H	240	...	$C_{19}H_{14}F_3NO_2$	4.05	3.99
COOH	C_2H_5	Br	280	...	$C_{19}H_{13}BrF_3NO_2$	3.30	3.32
COOH	n-C_3H_7	H	243	...	$C_{20}H_{16}F_3NO_2$	3.90	3.90
COOH	n-C_3H_7	Br	246	...	$C_{20}H_{15}BrF_3NO_2$	3.19	3.18
COOH	C_6H_5	H	262	...	$C_{23}H_{14}F_3NO_2$	3.56	3.50
COOH	C_6H_5	Br	318	...	$C_{23}H_{13}BrF_3NO_2$	2.95	3.00
H	H	H	74	160	$C_{16}H_{10}F_3N$	5.12	5.10
H	H	Br	82	212	$C_{16}H_9BrF_3N$	3.97	3.92
H	CH_3	H	84	177	$C_{17}H_{12}F_3N$	4.87	4.81
H	CH_3	Br	73	206	$C_{17}H_{11}BrF_3N$	3.82	3.82
H	C_2H_5	H	94	203	$C_{18}H_{14}F_3N$	4.65	4.64
H	C_2H_5	Br	56	196	$C_{18}H_{13}BrF_3N$	3.68	3.71
H	n-C_3H_7	H	38	145	$C_{19}H_{16}F_3N$	4.44	4.43
H	n-C_3H_7	Br	42	160	$C_{19}H_{15}BrF_3N$	3.55	3.49
H	C_6H_5	H	90	186	$C_{22}H_{14}F_3N$	4.01	4.02
H	C_6H_5	Br	102	171	$C_{22}H_{13}BrF_3N$	3.27	3.28

grams of VI, m.p. of 208° C. This product mixed with the products obtained in A and B had a m.p. of 208° C., and its infrared spectrum was identical with the spectra of the products mentioned in A and B. Anal. Calcd. for $C_{24}H_{12}F_9N_3$: C, 56.14; H, 2.33; F, 33.33; N, 8.18. Found: C, 56.20; H, 2.30; F, 33.02; N, 8.12.

Bis(*m*-trifluoromethyl)dibenzamide (VII). The methanol soluble fraction in C, after evaporation of a part of the solvent, crystallized as long, silky crystals which, after a second crystallization, had a m.p. of 175° C. The infrared spectrum of this product showed the characteristic absorption bands of carbonyl (amide) and NH. The product, treated with concentrated sodium hydroxide solution, gave ammonia and the sodium salt of *m*-trifluoromethylbenzoic acid. The H of the NH group is weakly acidic. The pure product (VII) obtained amounted to 5.5 grams. Anal. Calcd. for $C_{16}H_9F_6NO_2$: C, 53.18; H, 2.49; F, 31.57; N, 3.87. Found: C, 53.36; H, 2.51; F, 31.20; N, 3.91.

Tris(*m*-trifluoromethyl)tribenzamide. To a solution of 1 gram of VII in 5 ml. of anhydrous pyridine, 0.80 gram of *m*-trifluoromethylbenzoyl chloride was added with shaking. The mixture became warm, a crystalline precipitate appeared, and after a while the whole mixture became solid. It was kept overnight at room temperature, 4 ml. of ethanol were added and, when cooled, the mixture was filtered under suction and washed with a little cold ethanol. The product (VIII), which was sparingly soluble in absolute ethanol, was dissolved in a mixture of dioxane and dilute alcohol and recrystallized, m.p. 190°, in quantitative yield. Anal. Calcd. for $C_{24}H_{12}F_9NO_3$: N, 2.62. Found: N, 2.63.

β-Phenylbutyrophenone. Aluminum chloride (47 grams) was added to 150 ml. of anhydrous benzene, and 29 grams of vinylacetyl chloride (*3*) were added with stirring which was continued for 3 hours. The mixture was allowed to stand overnight at room temperature and then decomposed with ice and HCl, the benzene phase was separated, and the aqueous phase was extracted three times with fresh benzene (total 100 ml.). The combined benzene solutions were washed with aqueous sodium bicarbonate, and then with water, dried over magnesium sulfate, and stripped of the solvent under reduced pressure. The solid residue was allowed to crystallize from 70% acetic acid and gave, in almost quantitative yield, the product in the form of white, shiny plates, m.p. 72.5° C. This product, mixed with authentic β-phenylbutyrophenone (*1*), had a m.p. of 72.5° C. Semicarbazone, m.p. 164° C. This ketone did not give a benzylidene derivative and would not undergo the Pfitzinger reaction to give a quinolinecarboxylic acid deriva-

tive, even when the ethanol was replaced by *n*-butanol, and the refluxing time was extended.

Quinolinecarboxylic Acid Derivatives. To prepare the quinolinecarboxylic acids, 0.01 mole of the appropriate ketone and 0.01 mole of isatin (or 5-bromoisatin) were dissolved in a solution of 0.033 mole of KOH in 30 ml. of 96% ethanol. The mixture was treated under reflux for 24 hours, diluted with five times its volume of water, treated with charcoal and filtered. Then, acetic acid or HCl was added to the filtrate until a strong acid reaction was attained. The mixture was allowed to stand in a refrigerator until the quinolinecarboxylic acid was completely precipitated. The precipitate was dissolved in acetic acid and crystallized. The yield in all cases was 85 to 95%.

The quinolinecarboxylic acids containing CF_3 groups are more soluble in water than their analogs without CF_3 groups. The prepared quinolinecarboxylic acids are listed in Table II.

Quinoline Derivatives. The decarboxylation of the above acids was carried out in a test tube, heated gently on a moderate flame, until carbon dioxide was completely evolved. The cooled residue was dissolved in 96% ethanol, the solution was treated with charcoal and filtered. A saturated alcoholic solution of picric acid was added to the filtrate, and the base was converted into its picrate. The picrate was separated and added to a mixture of 20 times its weight of chloroform and the same amount of water. An excess of ammonia was added, and the aqueous layer which dissolved the ammonium picrate was decanted off. The chloroform layer was washed with water repeatedly until the wash water was no longer colored. Chloroform was then evaporated, and the residue was dissolved in dilute methanol and crystallized. Yield, 85 to 90%. The prepared quinoline derivatives are listed in Table II.

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Thermodynamics of Ionization of Aqueous Barbituric Acid and Substituted Barbituric Acids

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Heats of ionization of barbituric acid and several substituted barbituric acids in aqueous solution have been determined calorimetrically at 298° K. Ionization constants have been determined for 5-allylbarbituric acid and 5-methylbarbituric acid. Entropies of ionization of all the acids investigated are calculated by combination of ΔG° values derived from ionization constants with our ΔH° values.

THE THERMODYNAMICS of ionization of aqueous barbituric acid and several substituted barbituric acids was investigated as a continuation of a program to determine and interpret such data for a variety of organic acids. Specific reasons for interest in the particular acids investigated are: The 5,5-disubstituted acids and their salts in solution have proved useful as buffers in the biologically important pH range from about 6 to 9; di- and tri-substituted barbituric acids are important hypnotic agents; and it has been postulated that un-ionized barbituric acids penetrate living cells more readily than do the constituent ions (2).

A number of investigations that are considered later in this paper have been concerned with determination of pK values for various barbituric acids, but only one of these yielded pK values of sufficient accuracy at several temperatures to permit calculation of reliable ΔH° and ΔS° values.

EXPERIMENTAL

The calorimeter used is patterned after one previously described (7) except that a Mueller G-2 Bridge and HS galvanometer are used with a nickel wire resistance thermometer for temperature measurements. Also, the resistance thermometer and calibration heater are contained in a glass spiral filled with mineral oil rather than wound on a silver cylinder. All of the calorimetric work reported here was carried out with 950 ml. of water or solution in the calorimeter at 25.0 ± 0.1° C.

1-Methylbarbituric acid and 1,3-dimethylbarbituric acid were prepared as follows. Diethylmalonate and the appropriate methylurea were added to absolute ethanol in which sodium had been previously dissolved. After being refluxed for 12 hours, the mixtures were acidified with HCl and stored overnight in a refrigerator. The resulting substituted barbituric acids were recrystallized twice from 95% ethanol and then vacuum dried. The melting points were 132° C. for 1-methylbarbituric acid and 122° C. for 1,3-dimethylbarbituric acid. All of the other barbituric acids investigated were supplied by Benzol Products.

Sodium salts of 5,5-diallylbarbituric acid, 5-methylbarbituric acid, and 5-allylbarbituric acid were prepared by mixing equivalent amounts of the barbituric acid and sodium ethoxide, both in absolute ethanol solution. Bar-