TABLE I

ARYLALKYLIDENEMALONONITRILES

Ethylidenemalononitriles	Formula	Reaction time, hr.	Yield,[a] %	M. p.,[b] °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen[c] Calcd.	Nitrogen[c] Found
1-Phenyl-	$C_{11}H_8N_2$	12	70	94	...[d]	...	..	..	...	...
1-(*p*-Chlorophenyl)-	$C_{11}H_7N_2Cl$	10	75	96	65.19	65.49	3.46	3.50	13.83	14.06
1-(*p*-Fluorophenyl)[e]	$C_{11}H_7N_2F$	5	79	122	70.94	71.14	3.79	3.89	15.05	15.51
1-Xenyl-	$C_{17}H_{12}N_2$	2	74	159	83.56	83.34	4.96	4.93	11.47	11.73
1-(*p*-Nitrophenyl)-	$C_{11}H_7O_2N_3$	4	80	154	61.90	61.58	3.31	4.38	19.71	19.20
1-(*p*-Ethoxyphenyl)-	$C_{13}H_{12}ON_2$	2	78	88	73.56	73.58	5.70	5.79	13.18	13.47
1-(*p*-Tolyl)-	$C_{12}H_{10}N_2$	11	85	97	79.09	79.30	5.53	5.54	15.38	15.72
1-(2',5'-Dimethylphenyl)-	$C_{13}H_{12}N_2$	5	60	87	79.56	79.44	6.17	6.22	14.28	14.37
1-(*p*-Ethylphenyl)-	$C_{13}H_{12}N_2$	10	60	67	79.56	79.84	6.17	5.99	14.28	13.74
1-(*p*-Isopropylphenyl)[f]	$C_{14}H_{14}N_2$	4	63	..[g]	79.95	79.82	6.72	6.62	13.33	13.88
1-(*p*-*t*-Butylphenyl)-[f]	$C_{15}H_{16}N_2$	3	67	..[h]	80.31	80.29	7.19	7.10	12.48	12.83
1-(*m*-Ethylphenyl)-	$C_{13}H_{12}N_2$	7	61	67[i]	79.56	79.74	6.17	6.17	14.28	14.34
1-(3',5'-Diethylphenyl)-	$C_{15}H_{16}N_2$	6	60	83–84	80.31	80.43	7.19	7.54	12.48	12.38
1-(α-Thienyl)-	$C_8H_6N_2S$	8	71	86	61.71	62.14	4.03	3.56	15.99	15.90
Other Malononitriles										
1-Phenylbutylidene-	$C_{13}H_{12}N_2$	14	70	57	79.56	79.61	6.17	6.31	14.28	14.41
1-Phenylhexylidene-	$C_{15}H_{16}N_2$	16	61	..[i]	80.31	80.25	7.19	7.12	12.48	12.60
1,2,3,4-Tetrahydro-1-naphthylidene-	$C_{13}H_{10}N_2$	4	79	109	80.27	80.21	5.20	5.29	14.43	14.60

[a] Actually conversion. The yields were all in excess of 90% based on unrecovered ketone. [b] Taken with calibrated thermometers uncorrected for stem exposure. [c] By the micro Dumas method. Kjeldahl values were often somewhat low. [d] Mowry, *loc. cit.*, b. p. 122–124° (2 mm.). [e] *p*-Fluoroacetophenone obtained through the courtesy of Miss Mary Renoll. The condensation product had 10.38% F (calcd. 10.21%). [f] *p*-Isopropylacetophenone and *p*-*t*-butylacetophenone obtained through the courtesy of Dr. W. Frederick Huber. [g] B. p. 152–154° (2 mm.), $n^{25}D$ 1.5740. [h] B. p. 158–159° (2 mm.), $n^{25}D$ 1.5700. [i] Mixed m. p. with 1-(*p*-ethylphenyl)-ethylidenemalononitrile, 53–60°. [j] B. p. 154–156° (3 mm.), $n^{25}D$ 1.5484.

uct after the first recrystallization or first distillation. The solid products were then recrystallized, usually three or four times, to constant melting point. The crystalline malononitrile derivatives were all colorless or pale yellow needles with the exception of the α-tetralone condensation product which formed well-defined plates.

Summary

The effect of variation in structure and position of substituents of aryl alkyl ketones on their reaction rate in the Knoevenagel condensation with malononitrile has been studied. Sixteen new malononitrile derivatives are reported.

3,5-Diethylacetophenone has been prepared and an improved synthesis of 3,5-diethylbenzoic acid is described.

DAYTON, OHIO RECEIVED JANUARY 2, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Polymethylene-bis-(*p*-aminophenyl Sulfones)

BY H. B. CUTTER, C. A. DANIELSON AND H. R. GOLDEN

A series of polymethylene-bis-(*p*-aminophenyl sulfones) has been prepared with a view to their possible therapeutic use. However, since their preparation and properties have not previously been reported, it appears desirable to give a brief description of the work.

With the exception of the methylene derivative, the polymethylene-bis-(*p*-aminophenyl sulfones) are readily obtained by the action of the sodium salt of *p*-acetamidobenzenesulfinic acid on the corresponding alkyl dihalide in aqueous ethanol solution, followed by hydrolysis of the resulting acetamido compound to the free amine.

$$2\ CH_3CONHC_6H_4SO_2Na + Br(CH_2)_nBr \longrightarrow CH_3CONHC_6H_4SO_2(CH_2)_nSO_2C_6H_4NHCOCH_3 + 2NaBr$$

$$CH_3CONHC_6H_4SO_2(CH_2)_nSO_2C_6H_4NHCOCH_3 + H_2O(HCl) \longrightarrow H_2NC_6H_4SO_2(CH_2)_nSO_2C_6H_4NH_2\cdot 2HCl + 2CH_3COOH$$

The methylene compound could not be prepared by the condensation of sodium *p*-acetamidobenzenesulfinate with methylene bromide or iodide. One molecule of the salt reacted readily forming *p*-acetamidophenyl iodomethyl sulfone, but a second molecule of the salt could not be made to react. This is probably owing to the well-known effect of the sulfone group in deactivating alpha halogens toward double decomposition reactions.[1] The compound was

(1) Ziegler and Connor, THIS JOURNAL, **62**, 2596 (1940); Michael and Palmer, *Am. Chem. J.*, **6**, 254 (1884).

TABLE I

Name	Formula	M. p., °C.	Reflux., time, hr.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	% Sulfur Calcd.	% Sulfur Found
Methylene-bis-(*p*-acetaminophenyl sulfide)	$C_{17}H_{18}N_2O_2S_2$	212	4	98	8.09	8.06	18.51	18.50
Methylene-bis-(*p*-acetaminophenyl sulfone)	$C_{17}H_{18}N_2O_6S_2$	319		85	6.85	6.64	16.62	15.46
Methylene-bis-(*p*-aminophenyl sulfone)[a]	$C_{13}H_{14}N_2O_4S_2$	234		83			18.62	18.80
p-Aminophenyl iodomethyl sulfone	$C_7H_8INO_2S$	172	8	50	4.71	4.90	10.77	10.60
Ethylene-bis-(*p*-acetaminophenyl sulfone)	$C_{18}H_{20}N_2O_6S_2$	284	7	80	6.60	6.41	15.11	15.20
Ethylene-bis-(*p*-aminophenyl sulfone)[b]	$C_{14}H_{16}N_2O_4S_2$	328		90	8.23	8.18		
Ethylene-bis-(*p*-aminophenyl sulfone) dihydrochloride[b]	$C_{14}H_{16}N_2O_4S_2 \cdot 2HCl$	328		90			15.51	15.53
Trimethylene-bis-(*p*-acetaminophenyl sulfone)	$C_{19}H_{22}N_2O_6S_2$	244	8	75	6.39	6.41	14.62	14.54
Trimethylene-bis-(*p*-aminophenyl sulfone)	$C_{15}H_{18}N_2O_4S_2$	139		85	7.90	7.93	18.09	18.02
Trimethylene-bis-(*p*-aminophenyl sulfone) dihydrochloride[c]	$C_{15}H_{18}N_2O_4S_2 \cdot 2HCl$	230						
Tetramethylene-bis-(*p*-acetaminophenyl sulfone)[d]	$C_{20}H_{24}N_2O_6S_2$	266	12	85	6.19	5.96	14.17	14.17
Tetramethylene-bis-(*p*-aminophenyl sulfone)	$C_{16}H_{20}N_2O_4S_2$	289		90	7.60	7.51	17.40	17.62
Tetramethylene-bis-(*p*-aminophenyl sulfone) dihydrochloride[e]	$C_{16}H_{20}N_2O_4S_2 \cdot 2HCl$	289		90	6.34	6.24		
Pentamethylene-bis-(*p*-acetaminophenyl sulfone)[f]	$C_{21}H_{26}N_2O_4S_2$	157	8	40			13.74	13.60
	$C_{21}H_{26}N_2O_4S_2 \cdot C_2H_5OH$	75–77			5.49	5.29	12.51	12.67
Pentamethylene-bis-(*p*-aminophenyl sulfone)	$C_{17}H_{22}N_2O_4S_2$	116		90	7.33	7.38	16.76	16.64
Pentamethylene-bis-(*p*-aminophenyl sulfone) dihydrochloride[g]	$C_{17}H_{22}N_2O_4S_2 \cdot 2HCl$	246–248		90	6.15	6.29		

[a] The hydrochloride is water soluble and unstable. On heating it decomposes below 110°. [b] In this series many of the hydrochlorides have the same melting points as the free bases, because the hydrochlorides decompose to the free base below their melting points. This can be shown by heating the hydrochloride gently in a test-tube—a piece of moist congo red paper is turned blue when held above the heated solid. [c] Neutral equivalent, calcd. 213; found, 215. [d] In this case the halide used was 1,4-dichlorobutane, and an equivalent amount of potassium iodide was added to the mixture. [e] Neutral equivalent, calcd. 221; found, 214. [f] This compound crystallizes with one mole of ethanol of crystallization, m. p. 75–77°. On drying in a vacuum at 70° the ethanol is lost and crystals melting at 157° are obtained. [g] Neutral equivalent, calcd., 228; found, 232. [h] Fourneau, Tréfouel, Nitti and Bovet, *Compt. rend. soc. biol.*, **127**, 393 (1938), mention this compound but do not record its properties or method of preparation.

finally obtained by condensing *p*-acetamidothiophenol with methylene iodide or formaldehyde,[2] and oxidizing the resulting mercaptal to the disulfone.[3]

Experimental

Methylene-bis-(*p*-acetamidophenyl Sulfide).—(1) *p*-Acetamidothiophenol, 3.3 g., was dissolved in 100 ml. of ethanol containing 0.46 g. of sodium; 2.7 g. of methylene iodide was added and the mixture refluxed gently under an inert atmosphere for four hours. The mixture was cooled to room temperature and sufficient water added to precipitate the product as a yellowish-white solid. Recrystallization from 95% ethanol yielded white crystals, m. p. 212–213°; yield, 3.4 g. (98%).

(2) *p*-Acetamidothiophenol, 25 g. was suspended in a mixture of 6 ml. of 35% formalin and 50 cc. of glacial acetic acid. Dry hydrogen chloride gas was passed into the mixture until it was saturated, and the yellow solution placed in the ice box for twenty-four hours. The mercaptal separated as a yellowish-white solid. It was filtered off and washed with 50 ml. of glacial acetic acid. Recrystallization from 95% ethanol yielded 10 g. of white crystals, m. p. 211–212°.

Methylene-bis-(*p*-acetamidophenyl Sulfone).—Methylene-bis-(*p*-acetamidophenyl sulfide), 3.5 g., was suspended in 15 ml. of glacial acetic acid containing 6 ml. of 30% hydrogen peroxide. The mixture was cooled in ice for three to four hours and then allowed to stand at room temperature for twenty-four hours. The sulfone was precipitated by addition of 50 ml. of water. The sulfone was filtered, washed with cold water and dissolved in 250 ml. of 5% sodium hydroxide in which it is difficultly soluble. This solution was filtered and acidified with hydrochloric acid to precipitate the sulfone. The yield was 3.5 g. (83%) of white crystals, m. p. 319–320°.

Methylene-bis-(*p*-aminophenyl Sulfone).—Methylene-bis-(*p*-acetaminophenyl sulfone), 0.6 g. was suspended in 15 ml. of concentrated hydrochloric acid and warmed on the steam-bath until completely dissolved. The free amine was precipitated by neutralization with ammonium hydroxide. The yield was 0.4 g. (83%) of a white solid which easily turned yellow on standing, m. p. 234–235°.

p-Aminophenyl Iodomethyl Sulfone.—*p*-Acetamidobenzene sulfinic acid, 24 g., was dissolved in 200 ml. of 75% ethanol and exactly neutralized with sodium hydroxide. Then 16 g. of methylene iodide was added and the mixture refluxed for eight hours. A crystalline compound containing iodine separated. This was purified by recrystallization from 95% ethanol and refluxed with concentrated hydrochloric acid to convert it to the amine hydrochloride. Treatment with cold dilute sodium hydroxide yielded the free amino compound as white crystals, m. p. 172–173°

Ethylene-bis-(*p*-acetamidophenyl Sulfone).—*p*-Acetamidobenzenesulfinic acid, 60 g., was dissolved in 200 ml. of 75% ethanol and exactly neutralized by sodium hydroxide. Ethylene dibromide, 18.8 g., was then added and the mixture refluxed for eight hours. At the end of one hour a white solid separated. The mixture was not allowed to become alkaline during the refluxing as sodium hydroxide decomposes ethylene disulfones.[4] At the end of eight hours the solid was removed by filtration, washed with water and then with ethanol and dried. The yield was 50 g. of white solid, m. p. 270–275°. Recrystallization from ethylene glycol yielded white crystals, m. p. 284–285° with decomposition.

Ethylene-bis-(*p*-aminophenyl Sulfone) Dihydrochloride.—Ethylene-bis-(*p*-acetamidophenyl sulfone), 20 g., was refluxed for one hour with 350 cc. of concentrated hydrochloric acid. The resulting white solid was filtered through a fritted glass filter, washed with concentrated hydrochloric acid and then with ethanol and dried in an oven at 100°; yield, 18 g. of white crystals. m. p. 328–330° with decomposition.

Ethylene-bis-(*p*-aminophenyl Sulfone).—Ethylene-bis-(*p*-aminophenyl sulfone) dihydrochloride, 5.1 g., was suspended in 100 ml. of cold water and 1.2 g. of potassium hydroxide added. The mixture was thoroughly stirred, and dilute potassium hydroxide solution added drop by drop until the mixture was exactly neutral. The resulting white solid was filtered, washed with water, ethanol and

(2) Taylor, THIS JOURNAL, **57**, 1067 (1935).

(3) Pomerantz and Connor, *ibid.*, **61**, 3386 (1939).

(4) Stuffer, *Ber.*, **23**, 3226 (1890); Otto and Damköhler, *J. prakt. Chem.*, [2] **30**, 171, 321 (1884).

then ether and dried; yield, 4.3 g., m. p. 328–330° with decomposition.

The other members of the series were prepared in a similar manner. *p*-Acetamidobenzenesulfinic acid, 0.12 mole was dissolved in about 200 ml. of aqueous (50–75%) ethanol and exactly neutralized with sodium hydroxide; 0.05 mole of the alkyl dihalide was added and the mixture refluxed for from eight to twelve hours. If the acetamidophenyl sulfone had precipitated, it was removed by filtration, otherwise it was precipitated by pouring the mixture into 700 ml. of water. The crude material was purified by recrystallization from ethanol.

The hydrolysis to the aminophenyl sulfone dihydrochloride and to the free amine was carried out as described above.

We wish to thank Parke, Davis and Company for generously supplying the *p*-acetamidobenzenesulfonyl chloride and the pentamethylene bromide used in this work.

Summary

A series of polymethylene-bis-(*p*-acetamidophenyl sulfones) has been prepared. These have been hydrolyzed to the corresponding amino compounds and their properties recorded.

DETROIT, MICHIGAN RECEIVED APRIL 6, 1945

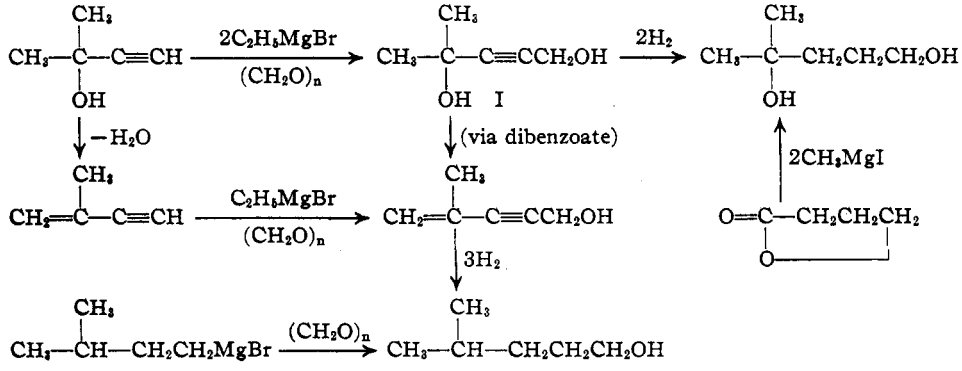
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Reaction of Bromomagnesium Derivatives of Acetylenic Alcohols with Formaldehyde

BY MELVIN S. NEWMAN, WILLIAM S. FONES[1] AND WILLIAM T. BOOTH, JR.

The organomagnesium compounds of acetylenic alcohols have been shown to react with a variety of carbonyl functions[2] including aldehydes (but not formaldehyde), ketones and carbon dioxide. In this paper we show that the dibromomagnesium compound of dimethylethynylcarbinol reacts smoothly with formaldehyde to yield 4-methyl-2-pentyne-1,4-diol,[3] I. This compound was characterized by means of its di-*p*-nitrobenzoate and a monotrityl derivative. On treatment with acetyl chloride and pyridine under conditions similar to those involved in the preparation of the di-*p*-nitrobenzoate, a monoacetate was formed. On catalytic reduction of I two moles of hydrogen were absorbed to yield 4-methyl-1,4-pentanediol authentic glycol made by treating butyrolactone with methylmagnesium iodide.[4]

The selective dehydration of the tertiary hydroxyl was accomplished by pyrolysis of the liquid dibenzoate of I. The structure of the resulting 4-methyl-4-penten-2-yn-1-ol obtained on hydrolysis was established by comparison with an authentic sample using the crystalline 3,5-dinitrobenzoate. The structure of the authentic 4-methyl-4-penten-2-yn-1-ol, prepared by treating 3-methyl-3-buten-1-ynylmagnesium bromide with formaldehyde, was supported by its method of synthesis and the absorption of 3 moles of hydrogen on catalytic reduction to form 4-methylpentanol-1. These reactions are summarized in the chart.



the structure of which was established by comparison of the di-*p*-nitrobenzoate with that of the

In addition to I, we have also prepared 3-(1-hydroxycyclohexyl)-2-propyn-1-ol by condensing the bromomagnesium derivative of 1-ethynylcyclohexanol with paraformaldehyde.

Experimental[5]

Dimethylethynylcarbinol.—In a 5-liter three-necked flask containing 2.5 liters of liquid ammonia and equipped with a sealed stirrer and an all-metal reflux condenser

(1) Part of the material herein presented was taken from the thesis presented by William S. Fones to the Ohio State University, 1942, for the M. A. degree.

(2) Ouvert, *Compt. rend.*, **146**, 294 (1908); Zalkind and Ivanov, *J. Gen. Chem., U. S. S. R.*, **11**, 803 (1941); Marvel and co-workers, THIS JOURNAL, **58**, 972 (1936); **61**, 2006 (1939); **62**, 1880 (1940); *J. Org. Chem.*, **7**, 93 (1942); Heilbron and co-workers, *J. Chem. Soc.*, 140, 141 (1944).

(3) A compound, b. p. 102–104° at 2 mm, made by condensing dimethylethynylcarbinol with aqueous formaldehyde has been reported, U. S. Patent 2,238,471 (1941), but no proof of structure was given.

(4) Henry, *Compt. rend.*, **143**, 1221 (1907).

(5) All melting points corrected. Analyses marked [a] by J. E. Varner, [b] by The Arlington Laboratories, Fairfax, Virginia, [c] by Sterling Olsen.