A Facile One-step Conversion of β- Benzoylacrylic Acids into Some Interesting Heterocycles and Study of their Microbiological Activity

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Summary: β-Aroylacrylic acids (**1-c**) have been reacted with thiourea, guanidine, and active methylene compounds and yielded thiopyrimidine derivatives (**2a-c**), aminopyrimidine derivatives (**5a** and **b**) and Michael adducts (**8-9**) respectively. The reactions of (**2**) and (**5**) with some electrophiles have been described.

Introduction

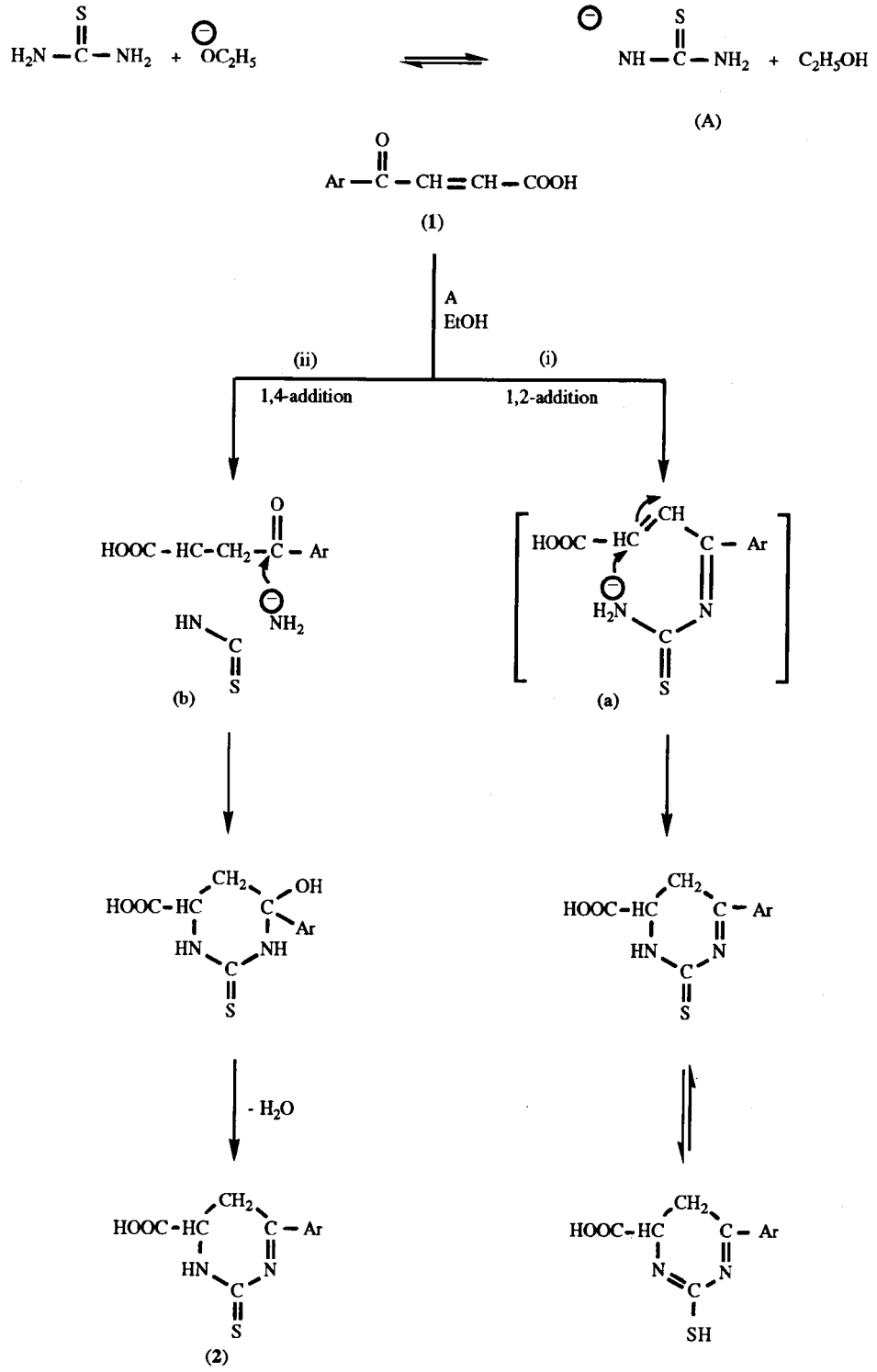
The reaction of acetylenic ketones with thiourea and its derivatives is known to give 4,6-diarylpyrimidine-2(2H)-thione derivatives [1,2]. The condensation of 1,3-diaryl-2-propen-1-ones with thiourea in the presence of sodium ethoxide under reflux for ten hours has been reported to give the corresponding 4,6-diaryl-5,6-dihydropyrimidine-2(2H)-thiones [3-5].

The present work as intended to study the reaction of β-aroylacrylic acids (**1a-c**) with thiourea, to throw more precise information on the course of the reaction.

Results and Discussion

It has been found that, thiourea reacts with β-benzoylacrylic acid in presence of dilute acetic acid and a slight excess of sodium carbonate forming 2-imino-4-oxo-5- phenylacyl thiazolidine [6]. When β-aroylacrylic acids (**1a-c**) were refluxed with thiourea in the presence of sodium ethoxide in ethanol for three hours, they gave the corresponding 6-aryl-4-carboxy-4,5-dihydropyrimidine-2-(1H)-thiones (**2a-c**). The reaction proceeds either by (i) 1,2-addition or (ii) 1,4-addition of the anion (A) to the ketonic moiety, followed by cyclization of the fleeting intermediates (a) and (b) (Scheme 1). Route (ii) seems more likely by analogy to the reaction of α,β-unsaturated keto acids with aromatic hydrocarbons [7] and active methylene compounds [8].

The structure of (**2**) was confirmed by elmental analysis and spectral data (cf. Table 1). The ^{1}H-NMR spectrum of **2c** (DMSO) showed signals at δ 3.2 (s, 3H, Ar-CH_3), 3.7 (m, 2H, CH_2), 4.2 (m, 1H methine proton) and 6.7 - 8.9 (m, 3H, Ar-H).



(Scheme 1).

Table 1: Physical and spectral data of prepared compounds Microanalysis Infrared spectrum

No.	M.p°C solvent	Yield %	M.F. M.Wt.	Calcd./Found C	H	N	S	ν_{CO}	$\nu_{C=N}$	$\nu_{NH\ and/or\ OH}$
2a	120	80	$C_{17}H_{14}O_3N_2S$	62.57	4.29	8.58	9.81	1720-1690	1620-1590	3460 (broad)
	A		326	62.62	4.33	8.60	9.70			
2b	240	85	$C_{11}H_8O_2N_2Cl_2S$	43.56	2.64	9.24	10.56	1710-1685	1610-1595	3450 (broad)
	A		303	43.72	2.73	9.44	10.62			
2c	155	90	$C_{12}H_{11}O_2N_2CIS$	50.97	3.89	9.91	11.32	1710-1690	1620-1595	3460 (broad)
	E		282.5	50.98	3.92	10.00	11.21			
3a	210	50	$C_{19}H_{16}O_4N_2S$	61.95	4.34	7.60		1710-1690 (COOH)	1600-1590	3350- 3420 (broad)
	But.		368	62.00	4.41	7.65		1680-1660 (ketonic)		
3b	222	50	$C_{14}H_{13}O_3N_2CIS$	51.77	4.00	8.62		1710-1685 (COOH)	1610-1595	3380- 3430
	But.		324.5	51.70	4.10	8.55		1680-1665 (ketonic)		
4a	220	30	$C_{17}H_{16}O_3N_4$	62.96	4.93	17.28		1640-1638	1590-1560	3420- 3320
	A		324	62.84	4.92	17.32				
4b	215	30	$C_{12}H_{13}O_2N_4Cl$	51.33	4.63	19.96		1650-1635	1580-1565	3430-3325
	E		280.5	51.39	4.87	20.20				
4c	104	30	$C_{17}H_{14}O_2N_4Cl_2$	54.11	3.71	14.85		1680 1640	3420-3220	
	T		377	54.01	3.68	14.80				
4d	224	60	$C_{17}H_{15}O_4N_3$	62.76	4.61	12.91		1670 1610	3420	
	A		325	62.72	4.61	13.10				
4e	145	60	$C_{11}H_9O_3N_3Cl_2$	43.71	2.98	13.90		1680 1600	3440	
	T		302	43.98	2.89	13.95				
4f	210	70	$C_{18}H_{17}O_4N_5$	58.85	4.63	19.07		1690(COOH)	1590 3420	
	T+E		367	58.71	4.66	18.92		1670 (amide)		
4g	215	60	$C_{18}H_{17}O_3N_5S$	56.39	4.44	18.54		1685(COOH)	1580 3400	
	A		383	56.40	4.47	18.60		1235(C=S)		
4h	115	60	$C_{12}H_{11}O_2N_5Cl_2S$	40.00	3.05	19.44	1685(COOH)		1590	3420
	T		360	39.93	3.00	19.54	1235 (C=S)			
5a	230	60	$C_{17}H_{13}O_3N_3$	66.44	4.23	13.68	1700		1600	3490-3200
	E		307	66.49	4.40	13.67				
5b	234	60	$C_{11}H_7O_2N_3Cl_2$	46.47	2.46	14.78	1800		1615	3480-3220
	E		284	46.52	2.50	14.72				
6a	216	65	$C_{19}H_{15}O_4N_3$	65.32	4.29	12.03	1720(COOH)		1590	3420
	E		349	65.29	4.23	11.97	1685 (CO amide)			
6b	222	60	$C_{13}H_9O_3Cl_2$	47.85	2.76	12.88	1715 (COOH)		1590	3440
	E		326	47.82	2.68	12.73	1675 (CO amide)			
6c	175	70	$C_{24}H_{17}O_4N_3$	70.07	4.13	10.20	1710(COOH)		1590	3460
	E		411	69.99	4.12	10.18	1685(CO amide)			
6d	121	70	$C_{18}H_{11}O_3N_3Cl_2$	55.67	2.83	10.82	1700 (COOH)		1600	3450
	T		388	55.78	2.91	11.03	1670 (CO amide)			
6e	178	70	$C_{24}H_{16}O_4N_3Cl$	64.64	3.59	9.42	1710(COOH)		1600	3420
	B		445.5	64.88	3.86	9.61	1680 (CO amide)			
7	230	60	$C_{25}H_{19}O_4N_3$	70.58	4.47	9.88	1680 1620 3255			
	E		425	69.99	4.30	10.01				
8	125	40	$C_{21}H_{20}O_6$	68.47	5.43	1665	(COOH)		--	3400
	T		368	68.47	5.40	1710	(COAr broad)			
9	135	40	$C_{21}H_{18}O_7$	65.96	4.71	1690	(COOH)			
	B		382	66.18	4.43	1720	(CO of ester and o-pyrone)		--	3410
10	281	40	$C_{19}H_{14}O_4N_2$	68.26	4.19	8.38	1700(CO of COOH)		1590	3300
	E		334	68.36	4.31	8.58	1630(CO of cyclic amide		2225(C=N)	

A = acetic acid, B = benzene, Bu = butenol, E = ethanol, T = toluene

The compound (2c) reacted with acetic anhydride to give the corresponding N-acetyl derivatives (3a,b). The ^{1}H-NMR spectrum of compound (3b) (DMSO) showed signals at 3.4-3.8 (s, 3H, $COOCH_3$), 3.9 (m, 2H, CH_2), 4.2 - 4.5 (m, 1H methine p;roton) and 7 - 8.3 (m, 3H, Ar-H).

Furthermore, (2) reacted with hydrazine hydrate, phenylhydrazine (in ethanol) hydroxylamine, semicarbazide and thiosemicarbazide (in ethanol/sodium hydroxide) to give the corresponding pyrimidine derivatives (4a-c). The ^{1}H-NMR spectrum of (4a) (DMSO) showed signals at δ 3.5 (m, 2H, CH_2), 4.7 - 4.9 (m, 1H, methine proton), 5.5 - 6.2 (m, 1H, NH) and 7 - 8 (m, 9H, Ar-H).

The reaction of α,β-unsaturated ketones with guanidine has been reported to give the corresponding 2-aminoaryl pyrimidine [4], for the present investigation the authors extend the study to include the reaction of β-aroylacrylic acids (1a,b) with guanidine hydrochloride as a preparative method of new pyrimidine derivatives (5a,b) to study their reactivity towards different electrophilic reagents and to account for the establishment of the mechanism of the reaction. The structure of (5a,b) was confirmed chemically by their reaction with acetic anhydride, benzoyl chloride and/or *o*-chlorobenzoyl chloride to yield N- acetyl (6a,b) or N-benzoyl derivatives (6c,d) and (6e) respectively. Furthermore, treatment of (5a) with anisaldehyde in boiling ethanol afforded the Schiff base (7).

It was reported [8] that β-aroylacrylic acids react with active methylene compounds under Michael conditions to give cyclic or normal Michael addition products depending on the nature of the active methylene compound. In this study, it was found that the reaction of β(*p*-phenoxy)benzoylacrylic acid (1a) with acetylacetone in boiling sodium methoxide, diethyl malonate in sodium methoxide (fusion and ethyl cyanoacetate in the presence of ammonium acetate in benzene gave (8), (9) and (10). Compound (10) was formed via 1,4- addition of active methylene compound followed by ring closure.

The characteristic physical and spectral data of compounds obtained are shown in the following Table 1-2.

Table 2: Physical data of microbiological activities

Compound No.	Antifungal Nystatin (120 μ/ml) Saccharomyces cervisiase	Antibiotic Neomycin (40 mg/ml) Bacillus pumilus	Antibiotic Tetracycline HCl (10 mg/ml) Micrococcus luteus
	I.Z.(mm) 27.5	I.Z.(mm) 20.3	I.Z. (mm) 26.7
2a	-ve	20.6	-ve
2b	-ve	10.4	-ve
2c	-ve	18.9	-ve
3a	-ve	11.4	-ve
4a	-ve	12.4	-ve
4b	-ve	19.2	16.7
5a	-ve	11.5	-ve
5b	-ve	21.5	13.4
6a	11.1	12.8	-ve
6b	-ve	13.7	-ve
10	-ve	13.7	-ve

Experimental

All melting points are uncorrected. The infrared absorption spectra are determined with Pye Unicam infrared spectrophotometer using KBr Wafer technique. The NMR spectra were recorded with the Varian (S-60T) instrument.

Reaction of β-aroylacrylic acids (1a-c) with thiourea; Formation of 2-thio-4,5-dihydro-6-arylpyrimidines (2a- c)

A mixture of (1a-c) (0.01 mole), thiourea (0.02 mole) and ethanol (15 ml) was treated with 10 drops of glacial acetic acid. The mixture was then heated under reflux for 4 hrs. The solid separated after cooling was crystallised from the suitable solvent (cf. Table 1).

Acetylation of (2a,c); Formation of N-acetyl-2-thio-4,5- dihydro-6-aryl-pyrimidines (3a,b)

A solution of (2a,c) (0.01 mole) in acetic anhydride (15 ml) was gently heated for 2 hrs. The solution was cooled, then poured into ice and the solid separated was crystallised from the appropriate solvent to give the corresponding acetyl derivatives (3a,b) (cf. Table 1).

Reaction of (2a-c) with hydrazine hydrate and phenylhydrazine; Formation of pyrimidinohydrazone (4a,b) and pyrimidinophenylhydrazone (4c)

A solution of (2a-c) (0.01 mole) in ethanol (20 ml) was heated with hydrazine hydrate, or phenyl-

Ac2O
RNH2
RCOCl
CH3COCH2COCH3
CH2(COOEt)2
NC-CH2-COOEt
(1a - c)
a; Ar = C6H5 - O - C6H4
b; Ar = 3,4 - Cl2(C6H3)
c; Ar = C6H3(CH3)Cl(2,5)
(2a - c)
a; Ar = C6H5 - O - C6H4
b; Ar = 3,4 - Cl2(C6H3)
c; Ar = C6H3(CH3)Cl(2,5)
(3a - b)
a; Ar = C6H5 - O - C6H4 -
b; Ar = C6H3(CH3)Cl(2,5)
(4a - h)
Ar R
a; C6H5 - O - C6H4 NH2
b; C6H3(CH3)Cl(2,5) NH2
c; 3,4 - Cl2(C6H3) HN - Ph
d; C6H5 - O - C6H4 OH
e; 3,4 - Cl2(C6H3) OH
f; C6H5 - O - C6H4 HN - CONH2
g C6H5 - O - C6H4 HN - CS - NH2
h 3,4 - Cl2 (C6H3) HN - CS - NH2
(5a, b)
a; Ar = C6H5 - O - C6H4
b; Ar = 3,4 - Cl2(C6H3)
(6a - e)
Ar R
a; C6H5 - O - C6H4 CH3
b; 3,4 - Cl2(C6H3) CH3
c; C6H5 - O - C6H4 C6H5
d; 3,4 - Cl2(C6H3) C6H5
e C6H5 - O - C6H4 C6H4 - Cl - O
(7)
Ar = C6H5 - O - C6H4
(8)
(9)
(10)

hydrazine (0.02 mole) under reflux for 3 hrs. The solid formed was crystallised from the suitable solvent to give pyrimidinohydrazone (**4a,b**) and pyrimidinophenylhydrazone (**4c**) respectively.

*Reaction of (**2a,b**) with hydroxylamine hydrochloride or with semicarbazide hydrochloride; Formation of oxime derivatives (**4d,e**) or semicarbazone derivatives (**4f**)*

To a solution of (**2a,b**) (0.01 mole) in ethanol (20 ml) was added hydroxylamine or semicarbazide (0.01 mole) and aqueous sodium hydroxide (0.02 mole). The cold mixture was shaken for one hour, then left at room temperature overnight. The solid separated was crystallised to give oxime or semicarbazone derivatives.

*Reaction of (**2a,b**) with thiosemicarbazide; Formation of thiosemicarbazone derivatives (**4g,h**)*

(i) In pyridine

A mixture of pyridine (30 ml), (0.01 mole) of (**2a**) and (0.01 mole) of thiosemicarbazide was heated under reflux for 6 hrs. after which was poured into ice - conc HCl mixture. The solid separated was crystallised to give (**4g,h**)

(ii) In sodium hydroxide

A mixture of (0.01 mole) of (**2b**) and (0.02 mole) sodium hydroxide in water (15 ml), was shaken with thiosemicarbazide (0.01 mole) for one hour, and then heated on a water bath for a further hour. The reaction mixture was poured into ice cold HCl, and the solid separated was crystallised to give (**4h**).

*Reaction of β-aroylacrylic acids (**1a,b**) with guanidine hydrochloride; Formation of 2-amino-6-(substituted phenyl)-4-carboxypyrimidine (**5a,b**)*

A mixture of β-aroylacrylic acid (**1a,b**) (0.05 mole) and guanidine hydrochloride (4.5 gm) in ethanol (100 ml) was refluxed while a solution of sodium hydroxide (0.15 mole) in water (15 ml) was added portionwise during 4 hrs. and the solution was further heated for 6 hrs. The solid formed, after cooling and pouring over ice cold HCl, was crystallised to give (**5a,b**).

*Acetylation of (**5a,b**); Formation of acetyl derivatives (**6a,b**)*

The pyrimidine (**5a**) or (**5b**) (0.01 mole) was refluxed with acetic anhydride (20 ml) for 2 hrs. The solid formed, after cooling, was crystallised to give the corresponding acetyl derivatives (**6a,b**)

*Reaction of pyrimidine (**5a,b**) with benzoyl chloride; Formation of 6-arylpyrimidine-2-benzamide derivatives (**6c,d**)*

The pyrimidine (**4a** and/or **b**) was heated under reflux with benzoyl chloride (0.01 mole) in ethanol (20 ml) for 2 hrs. The reaction mixture was poured onto ice and the obtained solid was crystallised from the suitable solvent to give (**6c,d**)

*Reaction of pyrimidine derivative (**5a**) with o-chlorobenzoyl chloride; Formation of (**6e**)*

A mixture of (**5a**) (0.01 mole) and o-chlorobenzoyl chloride (20 ml) was refluxed for 2 hrs on a water-bath. The solid formed, after cooling, was crystallised to give (**6e**).

*Reaction of pyrimidine derivative (**5a**) with anisaldehyde; Formation of Schiff base (**7**)*

A solution of pyrimidine (**5a**) (0.01 mole) in ethanol was refluxed with anisaldehyde (15 ml) for 2 hrs., and the solid formed on cooling, was crystallised to give (**7**).

*Base - catalysed addition of active methylene compounds to aroyl-acrylic acids; Formation of Michael adducts (**8-10**)*

(i) In sodium methoxide

A mixture of *p*-phenoxybenzoylacrylic acid (0.01 mole), acetyl-acetone or diethyl malonate (0.03 mole), and a solution of methoxide was fused on an oil-bath for 3 hrs. The aqueous layer was acidified with conc. HCl to give a solid which was crystallised from the proper solvent to give Michael adduct (**8**) and (**9**) respectively.

(ii) In ammonium acetate

A mixture of ethyl cyanoacetate (0.01 mole), *p*-phenoxy- benzoyl chloride (0.01 mole) and am-

monium acetate (0.02 mole) in benzene was heated under reflux for 8 hrs. The solid obtained was crystallised from the suitable solvent to give the pyridone (10).

Microbiological Activity

In the present work we are interested to study the biological activity of some organic compounds against different microorganisms namely, *Saccharomyces cerevisiae, Bacillus pumilus, Micrococcus luteus* compairing the effect with a standard antibiotics such as Nystatin (120 μ/ml), neomycin (40 mg/ml) and tetracycline hydrochloride (10 mg/ml) respectively. The biololgical tests are carried out on alcoholic extracts, the results obtained are tabulated, the negative control is zero, the inhibition zone as compared (mm) is 27.5, 20.6 and 26.7 respectively and the diameter of empty inhibition zone (I.Z) is 8.5 mm.

The same medium, assay organism and plates were used for the assay of nystatin, neomycin and tetracycline hydrochloride.

Medium

Medium No.5 Grove and Randall [9] also available as Difco Antibiotic Medium No. 5 was used. Each liter, adjusted to pH 8.0 ± 0.1 with NaOH, contained 6 gm of peptone, 3 gm of yeast extract, 1.5 gm of beef extract and 1.5 gm of agar.

Assay organism

A suspension of spores of *Bacillus pumilus, Micrococcus luteus* and *Saccharomyces cervisiae* - obtained according to the American Type Culture Correction, from Squibb Egypt Laboratories - were prepared essentially as described by Grove and Randall [9] for the antibiotic assay. The bacteria were grown on heart infusion (HI) agar (Difco Laboratories) in Roux bottles for 1 week at 37°C, and harvested with the use of distilled water and glass beads (4.55 mm diameter). The suspension was heated at 65°C for 30 minutes before and again after washing 3 times with sterile distilled water and finally resuspended in water at concentration of about 3×10^{10} colony forming units per milliliter. Such a suspension gave satisfactory results even after storage for 8 months.

Assay plates

The melted medium (50 - 52°C) was inoculated with the suspension of spores (0.5 % v/v) and 5 ml of the seeded medium was placed in each stainless steel petri dish and permitted to harden before storing in plastic bags at 4°C. Such plates could be used over a period of 4 weeks, but no after 8 weeks (due to germination of the spores during that interval).

Antibiotic standards

The antibiotics used for the preparation of the standards were obtained from Squibb Egypt Laboratories according to the American Type Culture Correction.

Procedure for the assay

For each assay, 0.02 ml of the sample is applied with a long-levy pipette to each of 4 paper discs (0.25 per inch). Similarly, concentration of the antibiotic standards (0.02 ml) is applied to 4 such dics. The discs are then placed on the surface of 2 seeded plates, 8 on each plate (2 of each of the 3 standard concentration and 2 of the "unknown" samples) evently spaced in a circle, with identical pairs opposite each other. The plates are promptly placed on level racks, preferably singly, but not more than two, in a 37°C incubator where they are left until a clear zone of inhibition appears; there can best be seen against a black background, or with transmitted light.

Readings and interpretation

The diameters of the zones are measured with a Helios vernier calipers to a tenth of a millimeter. For each plate, the mean diameter around each pair of the standard discs are plotted against the concentration of the standard discs on a semi-log paper and a dose-response curve is drawn through these points, which are usually in a straight line. When the point do not form a prefectly straight line, the greatest accuracy is achieved by connection of the actual points. The concentration of the "unknown" of each plate is determined by locating the point on the curve which represents the mean of the diameters of the zones of inhibition around the 2 discs on which the test serum was placed; the con-

centration, which corresponds to that diameters, is read off the ordinate. The final result for each sample is the mean of those concentrations derived from the readings of both plates. (cf. Table 2).

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