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SPECTROPHOTOMETRIC DETERMINATION OF PHENYLBUTAZONE AND OXYPHENBUTAZONE THROUGH CONDENSATION WITH P-DIMETHYLAMINOBENZALDEHYDE

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ABSTRACT

P-Dimethylaminobenzaldehyde is used for colorimetric determination of phenylbutazone and oxyphenbutazone both in pure form and in their tablets. The reaction proceeds via first formation of aldol intermediate which suffers aminolysis by piperidine with subsequent elimination to afford intensive and stable colored disubstituted styrene. Beer's law is obeyed in the range of 0.08-0.4 mg mg^{-1} for phenylbutazone and 0.08-0.24 mg ml^{-1} for oxyphenbutazone.

INTRODUCTION

Phenylbutazone and oxyphenbutazone are used for the treatment of painful symptoms associated with gout, rheumatoid arthritis, rheumatoid spondylitis and painful shoulder[1]. They were determined by bromometric titration, another method depends on titration with N-bromosuccinimide in acetic acid medium, also aqueous and non aqueous volumetric solution of sodium borohydride was used for their determination[2-4]. Spectrophotometric determination of these drugs were also reported in literature[5-10].

EXPERIMENTAL

Materials, Reagents and Standards:

- Authentic phenylbutazone (El-Nile Co.).
- Authentic oxyphenbutazone (El-Nile Co.).
- Standard phenylbutazone 1 mg ml^{-1} in ethanol.
- Standard oxyphenbutazone 1 mg ml^{-1} in ethanol.
- Authentic P-dimethylaminobenzaldehyde.
- Standard P-dimethylaminobenzaldehyde 1 $mgml^{-1}$ in ethanol.
- Piperidine (Aldrich Co.).
- Alkazone tablets: Labelled to contain 100 mg Phenylbutazone per tablet.
- Romaxin tablets: Labelled to contain 100 mg oxyphenbutazone per tablet.
- Silica gel for column chromatography.

Apparatus:

Perkin-Elmer Lambda 2 UV/Vis spectrophotometer was used. ^{1}HNMR and ^{13}C NMR spectra were carried out in pharmacy institute, Bonn University using ^{1}H NMR spectrometer T-60 (Varian).

A) Determination of phenylbutazone and oxyphenbutazon:

An accurately measured volumes of standard phenylbutazone solution (equivalent to 2-10 mg) or standard oxyphenbutazone solution (equivalent to 2-6 mg) were transfered into a 50 ml round flask. Exactly add 8 ml of standard P-dimethylaminobenzaldehyde for phenylbutazone or 6 ml for oxyphenbutazone, were added, completed to 25 ml with ethanol, then 0.2 ml piperidine for phenylbutazone and 0.5 ml for oxyphenbutazone, were added. The mixture was refluxed for 100 and 70 minutes for phenylbutazone and oxyphenbutazone respectively.

The absorbance was measured at λ386 nm for phenylbutazone and at λ381 nm for oxyphenbutazone against blank experiments similarly prepared omitting phenylbutazone or oxyphenbutazone. The concentration was calculated of phenylbutazone or oxyphenbutazone from a standard curve prepared by the same procedures.

B) Determination of phenylbutazone and oxyphenbutazone tablets:

An accurately weighed amount of powdered contents of Alkazone or Romaxin tablets equivalent to 50 mg phenylbutazone or oxyphenbutazone was transfered into a beaker, dissolved in ethanol, filtered into a 50 ml volumetric flask, completed to volume with ethanol.

Different volumes of phenylbutazone solution (equivalent to 2-10 mg) or oxyphenbutazone solution (equivalent to 2-6 mg) were transferred into a 50 ml round flask. The procedure was completed as mentioned before.

RESULTS

The above described procedures were applied to:

i) Different concentrations of phenylbutazone and oxyphenbutazone. results were compared with those of the official B.P. methods,[11,12] (Tables 1 & 2).

ii) Alkazone tablets, containing phenylbutazone and romaxin tablets containing oxyphenbutazone. The obtained results were compared with those of the official B.P. methods,[13,14] (Tables 3 & 4).

DISCUSSION

Reaction of phenylbutazone and oxyphenbutazone under the proposed condition using P-dimethylaminobenzaldehyde and piperidine afforded products of modified absorption, thus allowing appropriate determination of these drugs. It seemed that

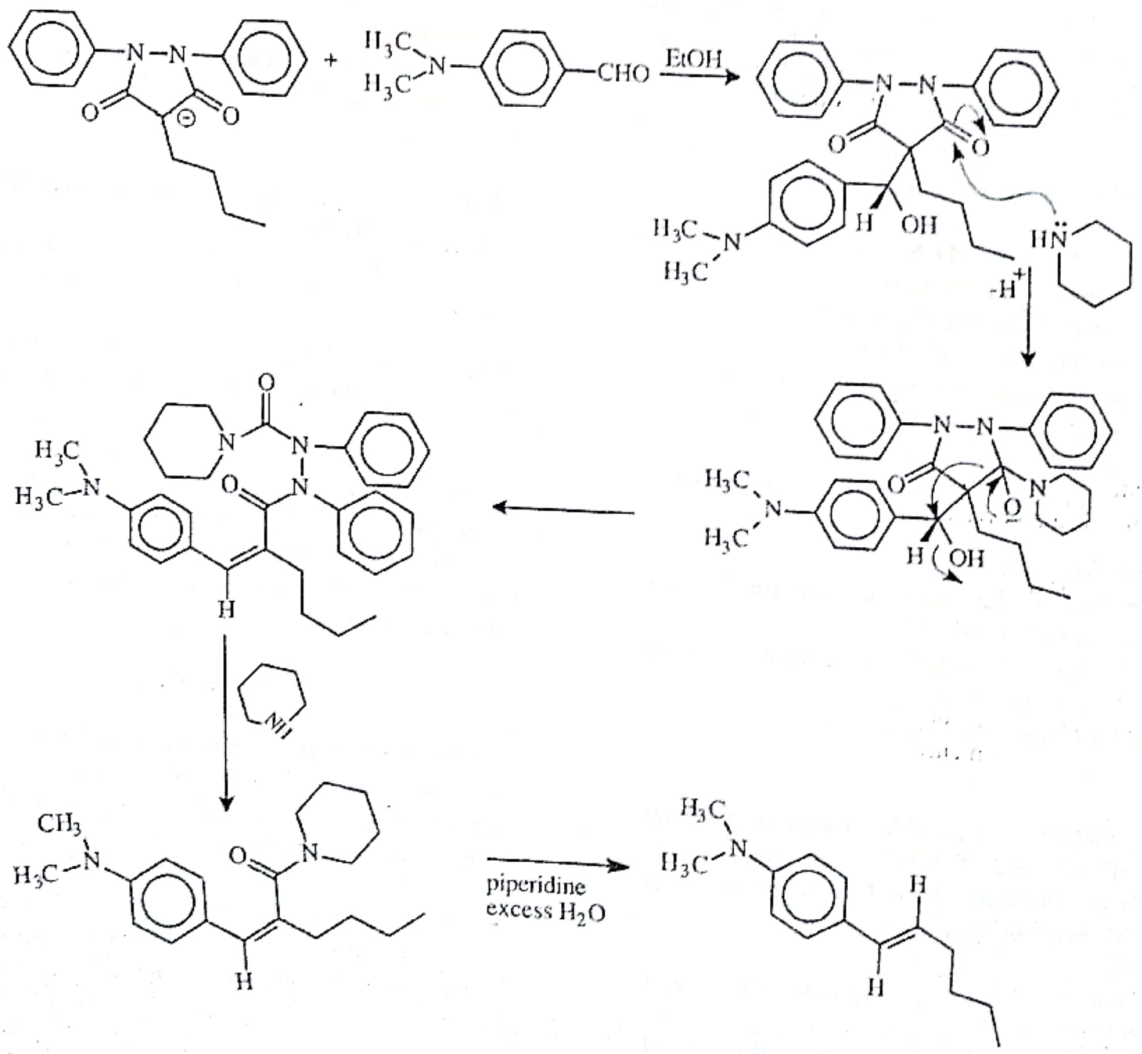
the reaction proceeds analogously to reaction of diazonium salt via first formation of Aldol intermediate which suffers aminolysis by piperidine with subsequent elimination to afford the stable intensively colored disubstituted styrene as shown in scheme 1:

These disubstituted styrenes have a yellow color which could be measured spectrophotometrically at 386 nm and 381 nm for phenylbutazone and oxyphenbutazone respectively.

Variables affecting the reaction were undertaken to develop maximum usefulness. Maximum absorption obtained when 8 ml of P-dimethylaminobenzaldehyde were added for phenylbutazone and 6 ml for oxyphenbutazone. Maximum absorption was obtained when phenylbutazone was condensed with aldehyde for 100 minutes and oxyphenbutazone for 70 minutes.

The effect of piperidine volume was experimentally studied, and 0.2 ml for phenylbutazone and 0.5 ml for oxyphenbutazone were found optimum. Beer's law was obeyed in the range of 0.08-0.4 $mgml^{-1}$ for phenylbutazone and 0.08-0.24 $mgml^{-1}$ for oxyphenbutazone (Fig. 1).

The molar ratio of phenylbutazone and oxyphenbutazone to P-dimethylaminobenzaldehyde were determined by continuous variation method,[15-17] which shows that the ratio is 1:1 for both phenylbutazone and oxyphenbutazone (Figs. 2&3).The color intensity of phenylbutazone and oxyphenbutazone with P-dimethylamino-benzaldehyde condensation products, was stable for one hour.



Scheme 1

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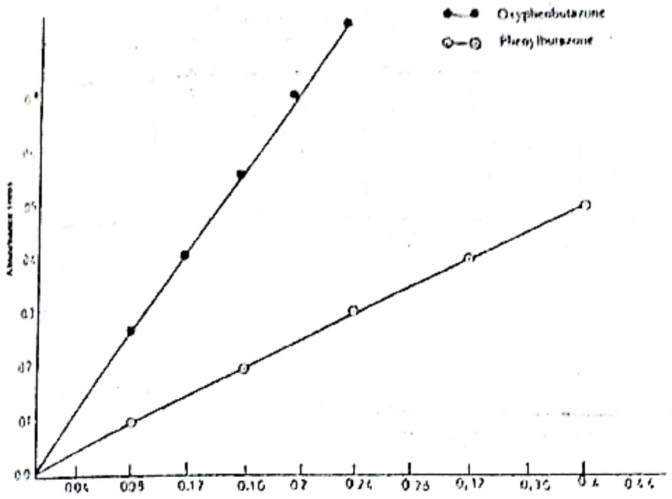

Concentration (mg/ml)

Fig. (1): Colibration curve for phenylbutazone and oxyphenbutazone- P - dimethyl-aminobenzaldehyde condensation compounds.

The proposed method was successfully applied for the determination of phenyl-butazone and oxyphenbutazone. Recovery % obtained by the official method is better than that of the proposed method, but our method is more sensitive and could be applied for smaller sample amounts, (Tables 1&2).Alkazone and Romaxin tablets were analysed by the suggested procedure.

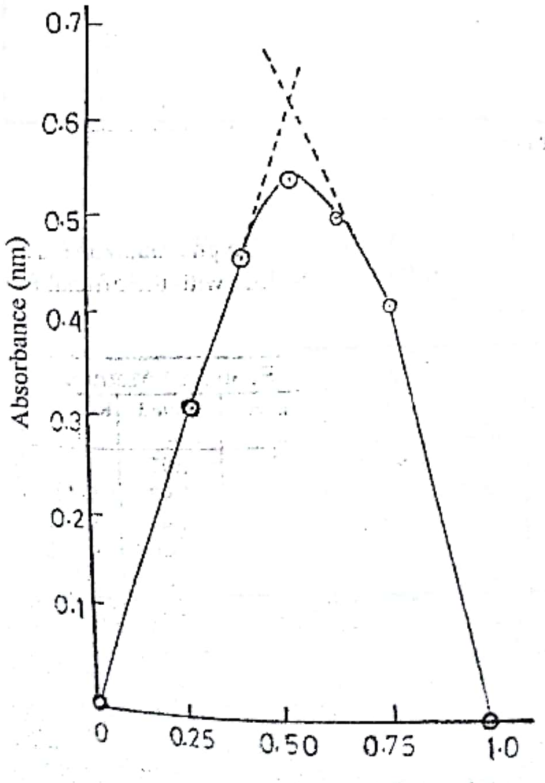

Fig. (2): Continuous variation plot of phenylbutazone (10^{-2}M)-P-dimethylaminobenzaldehyde (10^{-2}M) reaction.

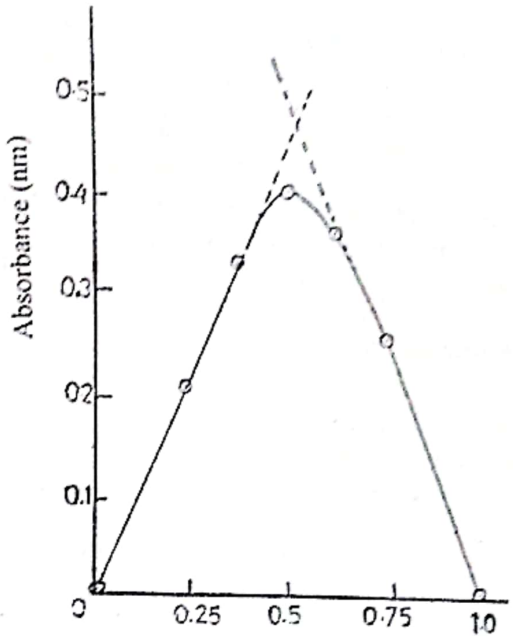

Fig. (3):Continuous variation plot of oxyphenbutazone ($2x10^{-3}$M) -P-dimethylaminobenzaldehyde ($2x10^{-3}$ M) reaction.

Tables (3&4) indicate that, the proposed method is more sensitive Than the official method, with sensitivity range (2-10 mg) for phenylbutazone and (2-6mg) for oxyphenbutazone compared with (50-250 mg) for the official method.

Statistical analysis of the results reveals that the suggested procedure is equally accurate and precise as the official method.

Isolation of the reaction products:

Column chromatography technique was used to separate the major reaction products.

Procedure for substance I:

The yellow-colored condensation product of phenylbutazone with P-dimethylaminobenzaldehyde was extracted with methylene chloride. Evaporation was carried out under reduced pressure, then chromatographed to give substance I, using (CH_2Cl_2. EtOH, 9:1) as a developing system.

Spectral analysis of subtance I:

The ^{1}HNMR spectral data of substance I show signals at 1.24 (tr., 3H; C.6) 1.65 (m, 2H; C-5), 2.05 (quin, 2H; C-4), 2.87 (m, 2H; C-3), 3.13 (S, 6H; $N(CH_3)_2$), 3, 72 (qr, 1H;C-2), 6.72 (d, 2H; C-8, 12) and 7.52 (d, 2H; C-9, 11).

^{13}C NMR spectral analysis of substance I:

^{13}C NMR spectrum of substance I, showed it 14 carbons, compared with 19 carbons for phenylbutazone and 9 carbons for P-dimethylaminobenzaldehyde. This spectrum has singals at δ 19.75 (C-6), 23.47 (C-5), 29.68 (C-4), 40.04 ($C_{13,14}$), 42, 40 (C-3), 111,80 (C- $_{8,12}$), 121,33 (C_{10}), 121, 69 (C_2), 134.86 ($C_{9,11}$), 152.88 (C_1) and 155.32 (C_7). The UV spectrum of substance I has λ max. at 447.8 nm.

Comparison of ^{1}HNMR spectrum of substance I, with those of phenylbutazone and P-dimethylaminobenz, revealed:

1- Absence of the multiplet signal at (δ: 7.3) due to aromatic protons of phenylbutazone.
2- Disappearance of the triplet singal at (δ : 3.4) of C-4 hydrogen of phenyl-butazone.
3- Presnece of the singlet signal at (δ: 3.1) integrating for [-N-$(CH_3)_2$] group of P-dimethyl-aminobenzaldehyde.

Spectral analysis of substance II:

Procedure for substance II:

The yellow colored condensation produce of oxyphenbutozone with P-dimethylaminobenzaldehyde was extracted with methylene chloride, evaporated under reduced pressure and chromatographed to give substance II using (CH_2Cl_2-EtOH, 8:2) as a developing system.

Spectral analysis of substance II:

The ^{1}HNMR spectral data of substance II show signals at 1.23 (tr., 3H: C-6), 1.40 (m, 2H; C-5), 1.97 (m, 2H; C-4), 2.85 (m, 2H; C-3), 3.10 (S, 6H; $N(CH_3)_2$), 3.70 (qr, H; C-2), 5.30 (S, H; C-1), 6.70 (d, 2H; $C_{(8,12)}$) and 7.50 (d, 2H, $C_{-(9,11)}$).

Comparison of ^{1}H NMR spectrum of substance II, with those of oxyphenbutazone and P-dimethylaminobenzaldehyde revealed:

i- Absence of the doublet signals at (δ= 6.6 87) and muttiplet signal at (δ = 7.3) due to aromatic protons of oxyphenbutazone.
ii- Disappearance of the tripl;et signal at (δ = 3.4) of C-4 hydrogen of oxyphenbutazone.
iii- Presence of the singlet signal at (δ = 3.1) integrating for [-N-$(CH_3)_2$] group of P-dimethylaminobenzaldehyde.

Table (1): Determination of phenylbutazone using the proposed method compared with the official B.P. (1988) method.

Official Method			Proposed Method		
Taken (mg)	Found (mg)	Recovery* (%)	Taken (mg)	Found (mg)	Recovery* (%)
50	49.96	99.92	2	1.98	99.47
100	100.53	100.53	4	3.95	98.95
150	149.80	99.87	6	5.99	99.94
200	199.84	99.92	8	7.85	98.23
250	248.12	99.25	10	9.96	99.59
Mean recovery ± S.D. (P = 0.05)		99.98 ± 0.45		99.24 ± 0.67	
N		5		5	
t				1.81 (2.30)	
F				2.15 (5.05)	

* Average of 3 experiments.

Table (2): Determination of oxyphenbutazone using the proposed method compared with the official B.P. (1988) method.

Official Method			Proposed Method		
Taken (mg)	Found (mg)	Recovery* (%)	Taken (mg)	Found (mg)	Recovery* (%)
50	49.81	99.62	2	1.97	98.38
100	100.86	100.86	3	2.97	98.98
150	148.98	99.32	4	3.99	99.74
200	1998.16	99.08	5	4.98	99.68
250	247.87	99.15	6	5.95	99.13
Mean recovery ± S.D. (P = 0.05)		99.61 ± 0.73		99.18 ± 0.56	
N		5		5	
t				1.05 (2.30)	
F				1.72 (5.05)	

* Average of 3 experiments.

Table (3): Determination of oxyphenbutazone in Alkazone using the proposed method and the official B.P. (1988) method.

Official Method			Proposed Method		
Taken (mg)	Found (mg)	Recovery* (%)	Taken (mg)	Found (mg)	Recovery* (%)
50	50.31	100.62	2	1.97	98.71
100	99.92	99.92	4	3.97	99.23
150	149.17	99.45	6	5.94	99.15
200	199.36	99.56	8	7.95	99.35
250	248.15	99.26	10	9.91	99.11
Mean recovery ± S.D. (P = 0.05)		99.79 ± 0.53		99.11 ± 0.24	
N		5		5	
t				2.62 (2.30)	
F				4.77 (5.05)	

* Average of 3 experiments.

Table (4): Determination of oxyphenbutazone using the proposed method compared with the official B.P. (1988) method.

Official Method			Proposed Method		
Taken (mg)	Found (mg)	Recovery* (%)	Taken (mg)	Found (mg)	Recovery* (%)
50	49.35	98.69	2	1.97	98.46
100	99.51	99.51	3	2.97	98.95
150	148.86	99.24	4	3.97	99.32
200	198.74	99.37	5	4.96	99.31
250	248.03	99.25	6	5.96	99.26
Mean recovery ± S.D. (P = 0.05)		99.21 ± 0.31		99.06 ± 0.37	
N		5		5	
t				0.70 (2.30)	
F				11.40 (5.05)	

* Average of 3 experiments.

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التقدير الطبيعى لمركب الفينيل بيوتازون والأوكس فينبيوتازون من خلال تفاعلهم مع ٤- ثنائى ميثيل أمينوبنزالدهيد

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قسم الكيمياء الصيدلية - كلية الصيدلة - جامعة الزقازيق

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فى هذا البحث تم تحليل كل من الفينيل بيوتازون والأوكس فينبيوتازمن بطريقة طيفية جديدة تعتمد على تفاعلهم مع ٤- ثنائى ميثيل أمينوا بنزالدهيد فى وجود البيبريدين.

وقد طلبت الطريقة المقترحة على المستحضرات الصيدلية (أقراص الالكازون والروماكسين)، وبمقارنة الطريقة المقترحة بالطريقة الدستورية وجد أن هذه الطريقة أكثر دقة ويمكن استخدامها فى تقدير كميات أصغر من المادة .