Aril Azines. II.[1] Hydrogenation of *p*-Tolil Monoazine

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Hydrogenation of *p*-tolil monoazine (**1***b*) over palladium-on-charcoal gives as the major product 4,5-dihydro-5-(*p*-toluyl)-3,4,5-tri-(*p*-tolyl)-1*H*-pyrazol-4-ol (**2***b*), which has previously been obtained by treatment of **1***b* with sodium methoxide. Several minor products are formed, which include *p*-tolualdehyde, *p*-toluic acid, and *p*-toluamide, *p*-tolunitrile, *p*-tolualazine, and 3,4,5-tri-(*p*-tolyl)-4*H*-pyrazol-4-ol (**9**). The structure of the last compound, which is also formed on reduction of **1***b* with sodium borohydride, was established by its independent synthesis from 1,2,3-tri-(*p*-tolyl)-1,3-propanedione by oxidation with lead tetraacetate followed by treatment with hydrazine. It is suggested that **2***b* arises via reduction of a C=N bond of **1***b* and aldol ring closure. The minor hydrogenation products are of interest in that their formation involves C—C hydrogenolysis; it is suggested that this is initiated by addition of a hydrogen atom to a carbonyl carbon atom of **1***b*.

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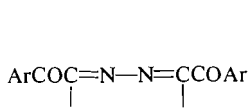
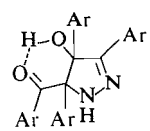
L'hydrogénation de la *p*-tolil monoazine (**1***b*) sur du palladium-sur-charbon conduit comme produit majeur au dihydro-4,5 *p*-toluyl-5 tri-*p*-tolyl-3,4,5 1*H*-pyrazolol-4 (**2***b*) qui avait été obtenu précédemment en traitant **1***b* par le méthylate de sodium. Plusieurs produits mineurs sont formés parmi lesquels on remarque la *p*-tolualdéhyde, l'acide *p*-toluique, la *p*-toluamide, la *p*-tolunitrile, la *p*-tolualazine et le tri-*p*-tolyl-3,4,5 4*H*-pyrazolol-4 (**9**). On a établi la structure du dernier composé, qui se forme aussi lors de la réduction de **1***b* par le borohydrure de sodium, par une synthèse non ambigue impliquant l'oxydation de la tri-*p*-tolyl-1,2,3 propanedione-1,3 par du tétraacétate de plomb et le traitement du produit obtenu avec l'hydrazine. On suggère que **2***b* provient de **1***b* par la réduction du lien C=N suivi d'une cyclisation aldolique. Les produits mineurs d'hydrogénation présentent de l'intérêt dû au fait qu'ils proviennent d'une hydrogénolyse d'un lien C—C; on suggère que cette réaction débute par l'addition d'un atome d'hydrogène sur l'atome de carbone du carbonyle de la molécule **1***b*. [Traduit par le journal]

Prolonged treatment of aril monoazines (**1**) with sodium methoxide has been shown to give phototropic products of type **2** (1). These products, which are dihydro derivatives of the azines, are formed in low yield (<25%). In order to obtain increased yields of these products we have investigated alternative methods of reduction of the azines. In preliminary experimentation it was found that benzil monoazine (**1***a*) is reduced to **2***a* by hydrogenation over palladium-on-charcoal.[2] We now report on an investigation of the hydrogenation of *p*-tolil monoazine (**1***b*).



1

a Ar = C_6H_5
b Ar = *p*-$CH_3C_6H_4$



2

a Ar = C_6H_5
b Ar = *p*-$CH_3C_6H_4$

Hydrogenation of **1***b* in benzene over 10% palladium-on-charcoal proceeded slowly with the uptake of *ca.* 4 molar-equiv. of hydrogen in *ca.* 30 h and gave as the major product the dihydro compound **2***b* in 56% yield.[3] This method is thus considerably more efficient and convenient than that involving treatment with sodium methoxide for the conversion of **1***b* to **2***b*.[4]

The hydrogenation of **2***b* also formed a number of other products in low yield. Several of these were compounds of known structure and were identified by direct comparison with authentic samples as *p*-tolualdehyde (**3**), *p*-toluic acid (**4**), *p*-toluamide (**5**), *p*-tolunitrile (**6**), and *p*-tolualazine (**7**). A crystalline product, m.p. 258–259°, isolated in too low a yield for full characterization is tentatively assigned structure

[1]For part I see ref. 1.

[2]We thank Dr. J. A. Weisbach for carrying out these experiments.

[3]The yield of this product was reduced if the hydrogenation was carried out for shorter periods.

[4]It has subsequently been found that the reduction of **1***b*–**2***b* is best effected by sodium in tetrahydrofuran (J. G. Smith and E. M. Levi, unpublished results).

8 on the basis of its spectra (see Experimental).

p-$CH_3C_6H_4COX$

3 X = H

4 X = OH

5 X = NH_2

p-$CH_3C_6H_4CN$

6

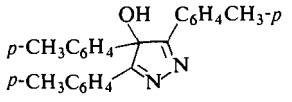
p-$CH_3C_6H_4CH{=}N\text{-}N{=}CHC_6H_4CH_3$-*p*

7

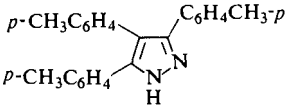
p-$CH_3C_6H_4COCHNHCOC_6H_4CH_3$-*p*
|
$C_6H_4CH_3$-*p*

8

A pale green crystalline product, $C_{24}H_{22}N_2O$, isolated in 4% yield, is of particular interest since it is also formed by treatment of the pyrazoline **2***b* with sodium borohydride. Its i.r. spectrum shows a band at *ca.* 3.0 μ, but no band in the carbonyl-stretching region, and its u.v. spectrum has a maximum at 342 nm (log ε 4.35). Structure **9** is assigned to this compound on the basis of these data and the observation that it is reduced by zinc and acetic acid to 3,4,5-tri-(*p*-tolyl)pyrazole (**10**), a product that is formed in addition to **9** in the reduction of **2***b* with sodium borohydride. Treatment of **9** with hot methanolic hydrochloric acid gave an isomeric yellow crystalline product in high yield that is considered to be the pyrazolone **11** formed by migration of a *p*-tolyl group.



9



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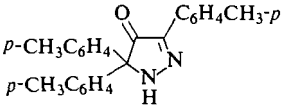


11

The structural assignment **9** was confirmed by an independent synthesis of this compound by the route shown in Scheme 1. Treatment of deoxy-*p*-toluoin (**12**) with sodium amide followed by *p*-toluyl chloride gave the 1,3-diketone **13** as the major product, accompanied by the *O*-acylation product **14** and the diacylation product **15**. Oxidation of **13** with lead tetraacetate in acetic acid gave the acetoxylation product **16**, which on treatment with hydrazine gave compounds **9** and **10**; the latter could arise via reduction of the former by hydrazine.

The catalytic hydrogenation of the azines of monocarbonyl compounds has been investigated extensively previously (2). Depending on the reaction conditions, reaction may involve saturation of one or both of the C=N bonds and hydrogenolysis of the N—N bond. In the present case the formation of the major product can be interpreted as proceeding via saturation of one of the C=N bonds of **1***b* to give **17** followed by an intramolecular aldol reaction to give **2***b* (Scheme 2, Ar = *p*-$CH_3C_6H_4$).

The minor products isolated from the hydrogenation reaction mixture are of interest in that their formation involves hydrogenolysis of one or more C—C single bonds. The formation of several of them can be rationalized in terms of a common radicaloid intermediate **18**, as shown in Scheme 3 (Ar = *p*-$CH_3C_6H_4$).[5] Others may arise via secondary reactions during work-up; *e.g.*, *p*-toluic acid (**4**) by air-oxidation of *p*-tolualdehyde and *p*-toluamide (**5**) by hydrolysis of *p*-tolunitrile.

The postulated hydrogenolysis of **1***b* to give the aldehyde **3** and the azines **19** and **7** finds some analogy in the C—C hydrogenolysis of β-diketones over Raney nickel to give aldehydes and ketones (3).

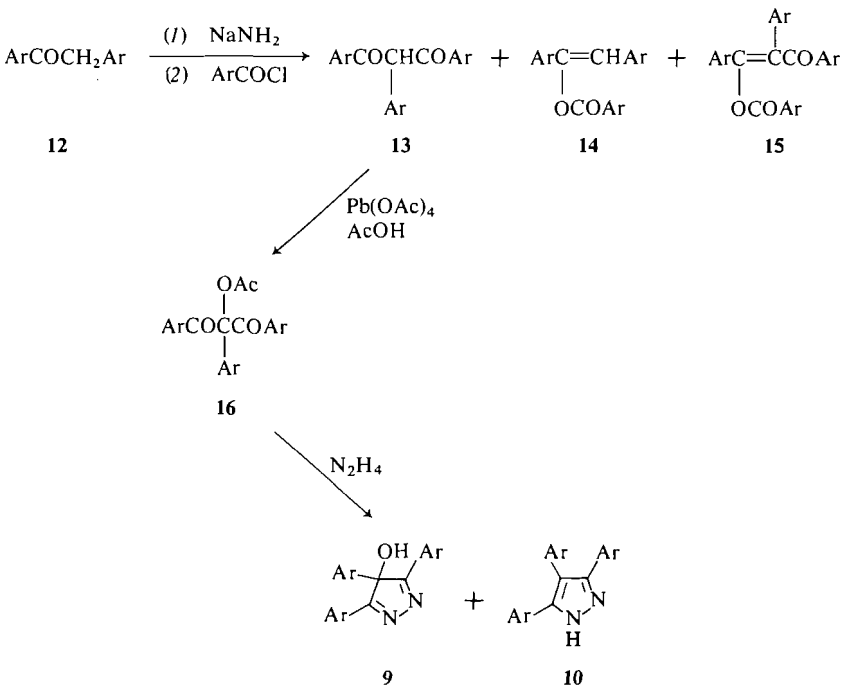
Experimental

Hydrogenation of p-Tolil Monoazine (1b)

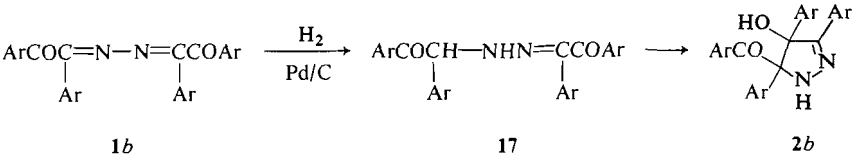
A solution of *p*-tolil monoazine (2.15 g) in hot dry benzene (thiophene free; 175 ml) was added to 10% palladium-on-charcoal (1.8 g) suspended in benzene (thiophene free; 20–40 ml) in an aluminum-foil-wrapped hydrogenation flask. Hydrogenation at atmospheric pressure led to the uptake of 500 ml (4.5 molar-equiv.) of hydrogen, which was complete in 34 h. The catalyst was removed at night under subdued light by filtration through sintered glass and the benzene solution was evaporated to give a red oil. This was taken up in ether (20 ml) and the solution was concentrated at room temperature to *ca.* 10 ml, giving crystalline compound **2***b*, m.p. 173–175° (dec.) (1.20 g; 56%), which was shown by i.r. and ^1H n.m.r. spectral comparison to be identical with the product obtained by treatment of **1***b* with sodium methoxide (1).

The residues (7.28 g) from four such hydrogenations of *p*-tolil monoazine (14.25 g) over 10% palladium-on-charcoal (12.41 g) with uptake of 3150 ml of hydrogen

[5]The radical species involved in this scheme are not considered to be free radicals but are viewed as remaining associated with the catalyst.



SCHEME 1



SCHEME 2

were combined after crystallization of compound **2***b* (7.27 g) and chromatographed on silica gel (540 g).

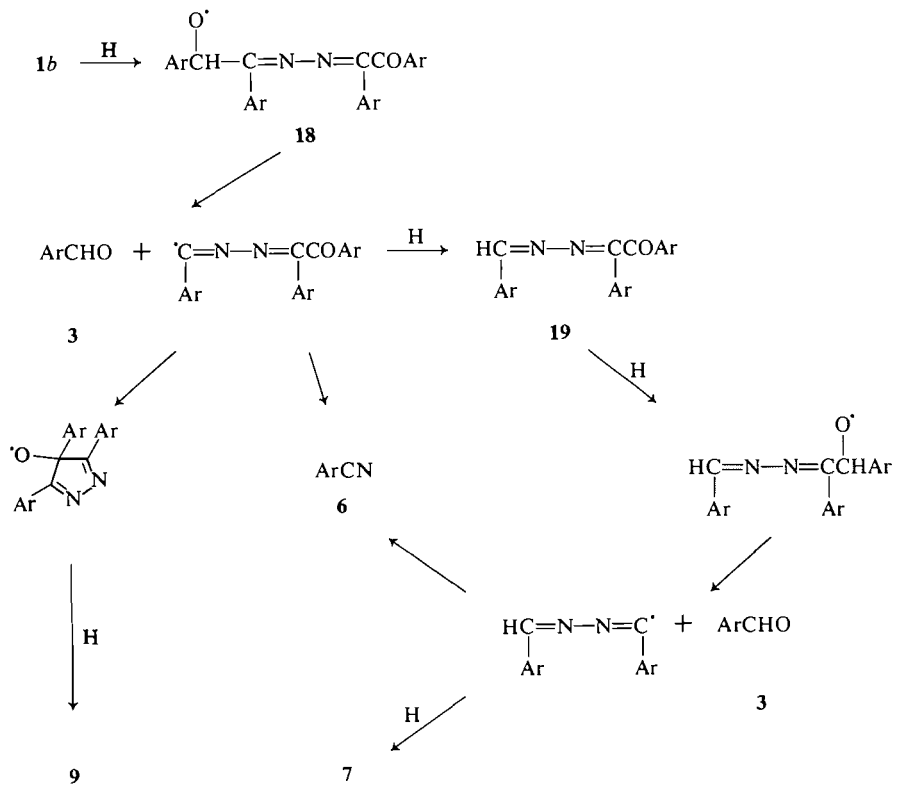
Elution with benzene – petroleum ether mixtures gave fractions containing less than 30 mg of material. Elution with benzene gave a semisolid fraction (30 mg), whose i.r. spectrum, with a band at 4.47 μ, showed it to contain *p*-tolunitrile.

Elution with ether–benzene (0.5:99.5) gave *p*-tolil monoazine (330 mg), followed by fractions containing *p*-tolil monoazine and *p*-tolualdehyde (940 mg), identified by i.r. spectroscopy. The formation of *p*-tolualdehyde was confirmed by examination of a fresh hydrogenation residue by v.p.c. and comparison of this chromatogram with a chromatogram of a mixture of this residue with authentic *p*-tolualdehyde. Further elution with the above solvent mixture gave *p*-tolil monoazine (160 mg) and fractions containing *p*-tolil monoazine and *p*-tolualazine (110 mg).

Elution with ether–benzene (1:99 and 2:98) gave an oil (470 mg) from which *p*-tolualazine (220 mg), m.p. 154–155.5° (lit. (4) m.p. 157–158°), crystallized from ethanol, after filtration of some *p*-tolil monoazine. It had λ_{max} ($CHCl_3$) 6.17, 6.23 μ; δ ($CDCl_3$) 2.35 (s, 6H), 7.20 (d, J = 8 Hz, 4H), 7.72 (d, J = 8 Hz, 4H), 8.62 (s, 2H). A mixture m.p. with an authentic sample, m.p. 157–158°, was 157–158°; the spectra of the two samples were indistinguishable.

Elution with ether–benzene (1:24 and 2:23) gave an oil (720 mg), which crystallized from ethanol–benzene to give a white solid (57 mg), m.p. 258–259°; λ_{max} ($CHCl_3$) 2.92, 5.85, 6.03 μ; *m/e*(%) 357(1), 341(2), 238(54), 221(36), 119(100). This product is tentatively assigned structure **8**.

Elution with ether–benzene (3:7 and 1:1) gave a semi-solid mixture (1.52 g), which was triturated with benzene to give a greenish tinged solid (470 mg), m.p. 206–208° (dec.). Recrystallization from methanol gave material, m.p. 209–211° (dec.), which was shown to be 3,4,5-*tri*-(*p*-tolyl)-4*H*-pyrazol-4-ol (**9**) (*vide infra*) by mixture m.p. and i.r. spectral comparison. Extraction of the benzene solution with aqueous sodium bicarbonate followed by acidification of the aqueous solution and extraction gave *p*-toluic acid (510 mg).



SCHEME 3

Elution with methanol–chloroform mixtures gave a white crystalline solid, m.p. 157–158°; λ_{max} ($CHCl_3$) 2.87, 2.98, 6.02 μ; *m/e*(%) 135(92), 119(100). This was identified as *p*-toluamide by mixture m.p. 158–160° with an authentic sample, m.p. 158.5–160°.

Reduction of **9** *with Zinc in Acetic Acid*

Compound **9** (20 mg) and zinc dust (148 mg) in acetic acid (30 ml) were heated under reflux with stirring until the original yellow color faded (3 h). The solution was filtered from unreacted zinc dust and the solvent was evaporated. The residue was taken up in hot methanol (*ca.* 3 ml), aqueous 10% sodium bicarbonate (4 drops) was added, and the solution was chilled to −20°. The crystalline product, m.p. 244–248°, had an i.r. spectrum indistinguishable from that of 3,4,5-tri-(*p*-tolyl)pyrazole (**10**) (1).

Acid-catalyzed Rearrangement of **9**

Compound **9** (104 mg) was added to a mixture of concentrated hydrochloric acid (3 ml) and methanol (50 ml) to give a dark yellow solution. This was heated under reflux for 1 day, cooled, and evaporated. The residue was taken up in chloroform and chromatographed on a silica gel t.l.c. plate (20 × 20 cm, 1 mm) developed with carbon tetrachloride. The major, deep yellow band (of seven) was extracted from the silica gel with chloroform. The residue obtained on evaporation of the extract was crystallized twice from aqueous methanol to give yellow needles, m.p. 151.5–153° (dec.); λ_{max} ($CHCl_3$) 2.98, 5.78, 5.87 μ; λ_{max} (EtOH) 250 nm (sh, log ε 4.10), 266 nm (log ε 4.16), 362 nm (sh, log ε 3.62), 393 nm (log ε 3.72); δ ($CDCl_3$) 2.27 (s, 6H), 2.33 (s, 3H), 7.0–7.2 (m, 10H), 7.45 (s, 1H, absent after D_2O treatment), 8.01 (d, J = 8 Hz, 2H); *m/e*(%) 354(3), 309(1), 219(50), 194(26), 140(62), 97(100).

Anal. Calcd. for $C_{24}H_{22}N_2O$: C, 81.32; H, 6.26; N, 7.90. Found C, 81.29; H, 6.55; N, 7.95.

1,2,3-Tri-(p-tolyl)-1,3-propanedione (13)

A crystal of ferric nitrate nonahydrate and sodium (4.4 g) were added to liquid ammonia (*ca.* 100 ml) in a three-necked flask, fitted with a Dry-Ice condenser, a double surface ether condenser, and a gas inlet tube. The solution was stirred for 30 min. Dry ether (100 ml) was added after removal of the Dry-Ice condenser and the flask was allowed to come to room temperature, the excess ammonia being removed by a stream of dry nitrogen. The ethereal suspension was heated under reflux for 5 min. A suspension of deoxy-*p*-toluoin (11.2 g) in dry ether (250 ml) was added and the mixture was heated under reflux for 6 h, cooled, and forced by nitrogen pressure into a pressure-equalized dropping funnel, whence it was added to a rapidly stirred solution of *p*-toluyl chloride (7.78 g) in dry ether (50 ml). The reaction mixture was stirred overnight and then treated with dilute hydrochloric acid (*ca.* 5%; 200 ml). The ethereal solution

was separated and the aqueous solution was extracted with fresh ether (200 ml). The ethereal solution was dried and evaporated. The residue was crystallized from absolute ethanol (500 ml) to give a white crystalline solid, m.p. 170–190°. This was treated with hot absolute ethanol to give a solution which upon cooling deposited a white crystalline solid (2.16 g), m.p. 168–170°. The residue (1.54 g) had m.p. 189–194°.

The solid, m.p. 168–170°, was recrystallized twice from absolute ethanol to give 1-(*p*-toluyloxy)-1,2-di-(*p*-tolyl)ethylene (**14**), m.p. 171–172°; λ_{max} ($CHCl_3$) 5.79, 6.06 μ (w); δ ($CDCl_3$) 2.24 (s, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 6.72 (s, 1H), 7.0–7.6 (m, 10H), 8.12 (d, J = 8 Hz, 2H); *m/e*(%) 342(2), 341(7), 119(100).

Anal. Calcd. for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 84.08; H, 6.59.

The solid, m.p. 189–194°, was twice recrystallized from absolute ethanol to give 3-(*p*-toluyloxy)-1,2,3-tri-(*p*-tolyl)-2-propen-1-one (**15**), m.p. 194–195°; λ_{max} ($CHCl_3$) 5.79, 6.02 μ; δ ($CDCl_3$) 2.24 (s, 6H), 2.28 (s, 6H), 6.9–7.4 (m, 12H), 7.68 (d, J = 8 Hz, 2H), 7.97 (d, J = 8 Hz, 2H); *m/e*(%) 460(9), 341(1), 119(100).

Anal. Calcd. for $C_{32}H_{28}O_3$: C, 83.45; H, 6.13. Found: C, 83.36; H, 6.25.

The original ethanolic mother liquor was concentrated to 75 ml and cooled. A white crystalline product (7.38 g), m.p. 130–145°, was isolated. Seven crystallizations from ethanol gave 1,2,3-tri-(*p*-tolyl)-1,3-propanedione (**13**), m.p. 147–148°; λ_{max} ($CHCl_3$) 5.90, 5.99 μ; δ ($CDCl_3$) 2.27 (s, 3H), 2.32 (s, 6H), 6.54 (s, 1H), 7.0–7.6 (m, 8H), 7.90 (d, J = 8 Hz, 4H); *m/e*(%) 342(18), 119(100).

Anal. Calcd. for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 84.07; H, 6.32.

3,4,5-Tri-(p-tolyl)-4H-pyrazol-4-ol (9)

1,2,3-Tri-(*p*-tolyl)-1,3-propanedione (**13**; 2.06 g) and lead tetraacetate (9.5 g) were stirred in glacial acetic acid (80 ml) for 6 days. The reaction mixture was poured into water. The solid that precipitated was separated by filtration through sintered glass and washed well with water. The filter cake was extracted with chloroform and these extracts were dried, filtered, and evaporated. The product, a yellow oil (2.49 g), was taken up in benzene and the solution was chromatographed on silica gel (100 g). Elution with ether–benzene (1:99 and 3:97) gave 2-acetoxy-1,2,3-tri-(*p*-tolyl)-1,3-propanedione (**16**) as a yellow oil (1.24 g); λ_{max} (CCl_4) 5.76, 5.98, 8.1–8.2 μ; δ (CCl_4) 1.92 (s, 3H), 2.22 (s, 9H), 6.85–7.15 (m, 6H), 7.33 (d, J = 8 Hz, 2H), 7.63 (d, J = 8 Hz, 4H).

Compound **16** (830 mg), without further purification, and hydrazine (95+%; 300 mg) were stirred in benzene solution (50 ml), containing acetic acid (2 drops) at room temperature. After 3 h crystals appeared in the solution; stirring was continued for 3 days. The crystalline product (230 mg) was filtered; m.p. 198–200° (dec.). Two recrystallizations from methanol gave 3,4,5-tri-(*p*-tolyl)-4*H*-pyrazol-4-ol (**9**), m.p. 211.5–212° (dec.); λ_{max} (KBr) 3.0, 6.22, 6.62 μ; λ_{max} (EtOH) 342 nm (log ε 4.35); *m/e*(%) 354(13), 338(9), 326(4), 237(17), 194(14), 119(25), 118(100), 91(19).

Anal. Calcd. for $C_{24}H_{22}N_2O$: C, 81.52; H, 6.26; N, 7.90. Found: C, 81.05; H, 6.27; N, 8.30.

Evaporation of the benzene filtrate and crystallization of the residue from methanol gave 3,4,5-tri-(*p*-tolyl)pyrazole (**10**) (50 mg), m.p. 232–237°. Two recrystallizations from methanol gave material, m.p. 252–252.5°; mixture m.p. 252.5–253° with an authentic sample, m.p. 253.5–254° (1).

Reduction of 2b with Sodium Borohydride

Compound **2***b* (1.00 g) and sodium borohydride (196 mg) were stirred in tetrahydrofuran–water (9:1; 100 ml) for 12 h. The aqueous layer was separated and the organic layer was dried. Acetyl chloride (2 ml) was added, and the solution was stirred for a few minutes and then poured into water. The aqueous layer was separated and extracted with ether. The ethereal and tetrahydrofuran solutions were combined, dried, and evaporated to give a yellow oil (834 mg), which was taken up in benzene and chromatographed on silica gel (40 g).

Elution with benzene gave 3,4,5-tri-(*p*-tolyl)-4H-pyrazol-4-ol (**9**) (110 mg) as a green tinged solid; crystallization from methanol gave needles, m.p. 209–211° (dec.); mixture m.p. 211–212° (dec.) with an authentic sample, m.p. 211.5–212° (dec.) (*vide supra*).

Elution with ether–benzene (1:4) gave 3,4,5-tri-(*p*-tolyl)pyrazole (**10**) (50 mg), m.p. 243–249°, identified by i.r. spectral comparison.

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