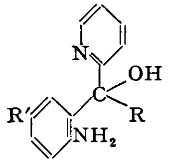
105. *Some* o-*Aminophenyl-pyridyl- and -quinolyl-carbinols.*

By A. J. Nunn and K. Schofield.

The reactions of 2-pyridyl- and 3-pyridyl-lithium with *o*-aminoacetophenone and related compounds to give 2-aminophenyl-pyridylcarbinols are described. 4-*o*-Aminobenzoylpyridine reacts normally with Grignard reagents. A further study of the reaction between 2-amino-4′-methoxybenzophenone and 2-pyridylmethyl-lithium (Schofield, *J.*, 1949, 2408) has been made, and reactions between the latter, and also 2-quinolylmethyl-lithium, and other 2-aminobenzophenones have been carried out.

Carbinols of the types (I—V) were required for synthetic work in the cinnoline series. Preliminary experiments on the preparation of a few such compounds have already been described (Schofield, *J.*, 1949, 2408). Thus 1-*o*-aminophenyl-1-2′-pyridylethanol (I; R = Me, R′ = H) and 1-*o*-aminophenyl-2-phenyl-1-2′-pyridylethanol (I; R = Ph·CH_2, R′ = H) were obtained by treating 2-*o*-aminobenzoylpyridine (VI) with the appropriate Grignard reagents. The carbinols (IV; R′ = H, R = Ph, or MeO·C_6H_4) and (V; R = H, R = Ph, and MeO·C_6H_4) were prepared from 2-aminobenzophenone or 2-amino-4′-methoxybenzophenone by the action of 2-pyridylmethyl- or 2-quinolylmethyl-lithium.



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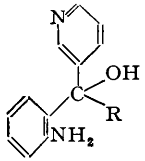

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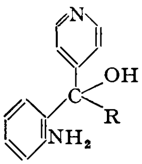

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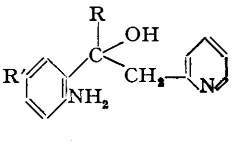

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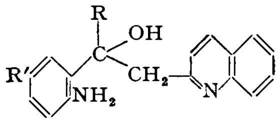

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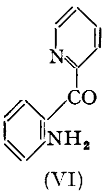

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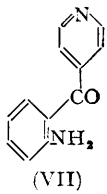


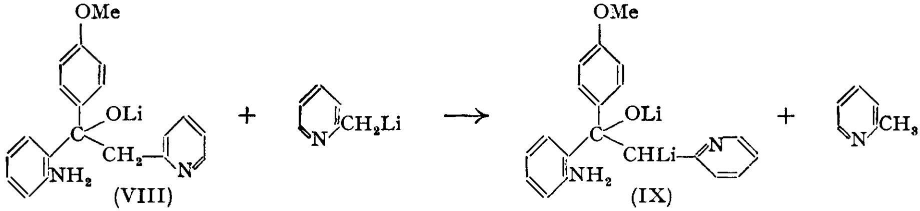
(VII)

This paper describes a more convenient route to compounds of the type (I) and its application to the preparation of carbinols (II). Further, a synthesis of compounds represented by (III) is given. Also, the preparation of the carbinols (IV) and (V) mentioned above has been re-examined, and new examples have been obtained.

Whilst the ketone (VI) reacts satisfactorily with Grignard reagents it is so inaccessible (see the preceding paper) as to make an alternative and more flexible method of synthesising the carbinols (I) essential if they are to be available in any number. A range of substituted *o*-aminoacetophenones and *o*-aminopropiophenones is now readily obtainable (Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1945, 646; Keneford and Simpson, *J.*, 1948, 354; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405) and we have found it convenient to treat these with the little used 2-pyridyl-lithium. The formation of this reagent in 62% yield, by halogen-metal exchange between 2-bromopyridine and *n*-butyl-lithium, has been described by Spatz (*Iowa State Coll. J. Sci.*, 1942—1943, **17**, 129) according to whom the chief difficulty arises from the tendency of *n*-butyl-lithium to add to the azomethine linkage of the pyridine derivative, but under suitable conditions this is rendered negligible, as shown by Adamson and Billinghurst (*J.*, 1950, 1039). The latter authors treated certain alkyl ketones with four equivalents of 2-pyridyl-lithium and obtained carbinols in good yield. Using, for economy, two equivalents of 2-pyridyl-lithium we have prepared (I; R = Me, R′ = H) in 42% yield from *o*-aminoacetophenone. In similar processes the appropriate ketones gave (I; R = Me, R′ = Cl) and (I; R = Et; R′ = H). Likewise, 3-pyridyl-lithium (Gilman and Spatz, *J. Amer. Chem. Soc.*, 1940, **62**, 446) reacted with *o*-aminoacetophenone and *o*-aminopropiophenone to form (II; R = Me) and (II; R = Et) respectively.

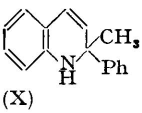
Unfortunately 4-pyridyl derivatives would appear not to be accessible by similar methods. 4-Pyridyl-lithium seems not to have been prepared and would probably be highly susceptible to addition to the pyridine–azomethine linkage. In the same way, attempts to prepare 4-pyridylmethyl-lithium gave addition products (cf. Prijs, Lutz, and Erlenmeyer, *Helv. Chim. Acta*, 1948, **31**, 571). For this reason we have used 4-*o*-aminobenzoylpyridine (VII) (Nunn and Schofield, preceding paper) as a source of carbinols of type (III). The ketone reacted readily with methyl- and ethyl-magnesium iodides, giving (III; R = Me and Et).

We extended our earlier incomplete work (Schofield, *loc. cit.*) on the reaction of 2-aminobenzophenone and 2-amino-4′-methoxybenzophenone with 2-pyridylmethyl- and 2-quinolylmethyl-lithium. By use of about one equivalent each of the lithium reagent and the ketone there were obtained originally 30% of (IV; R = Ph, R′ = H), 23% of (V; R = Ph, R′ = H), 26% of (IV; R = MeO·C_6H_4, R′ = H; owing to an error in transcription the yield appeared in print as 49%), and 35% of (V; R = MeO·C_6H_4, R′ = H). In the present work (IV; R = MeO·C_6H_4, R′ = H) was chosen for the chief examination, because its sparing solubility makes its isolation easy. It was first established that in the reaction between equivalent quantities of 2-amino-4′-methoxybenzophenone and 2-pyridylmethyl-lithium the material not accounted for previously was present as unchanged ketone, and not, as had seemed possible, as the ethylene formed by dehydration of the carbinol. A possible explanation of the low yield of the latter seemed to be that the intermediate (VIII) formed in the reaction might be capable itself of consuming 2-pyridylmethyl-lithium [to give (IX)], and so of preventing that reagent from attacking the ketone:

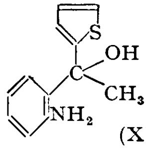


↓ Hydrolysis

(IV; R = MeO·C_6H_4, R′ = H)



(X)



(XI)

We therefore examined the method of "alternate additions" (Weiss and Hauser, *J. Amer. Chem. Soc.*, 1949, **71**, 2023; P. M. Foreman, Thesis, Univ. Stanford, 1943, "The Acylation and Aroylation of α- and γ-Alkylquinolines"). The procedure is exemplified in the Experimental section, but unfortunately the results were inexplicably erratic and no unambiguous improvement can be claimed.

We subsequently noticed that the use of two and three equivalents of 2-pyridylmethyl-lithium with 2-amino-4′-methoxybenzophenone raised the recovery of the carbinol to 51% and 78% respectively. The use of two equivalents of the reagent similarly improved the efficiency of the reaction with 2-aminobenzophenone. Therefore, as a compromise between efficiency and economy, we used two equivalents of the lithium reagent to one of the ketone in all subsequent experiments. 2-Amino-4′-methyl- and 2-amino-5-chlorobenzophenone thus provided 1-*o*-aminophenyl-2-2′-pyridyl-1-*p*-tolyl- (IV; R = Me·C_6H_4, R′ = H) and 1-(2-amino-5-chlorophenyl)-1-phenyl-2-2′-pyridyl-ethanol (IV; R = Ph, R′ = Cl).

The use of excess of the lithium reagent also led to increased recovery of (V; R = Ph, R′ = H) and (V; R = MeO·C_6H_4, R′ = H), and we now describe the further examples, 1-*o*-aminophenyl-2-2′-quinolyl-1-*p*-tolyl- (V; R = Me·C_6H_4, R′ = H) and 1-(2-amino-5-chlorophenyl)-1-phenyl-2-2′-quinolyl-ethanol (V; R = Ph, R′ = Cl). The lower yields obtained in the preparation of the quinolyl-, as compared with the pyridyl-carbinols, may be due to the tendency for addition reactions to occur at the quinaldine–azomethine linkage. Thus, Leonard and Boyer (*J. Amer. Chem. Soc.*, 1950, **72**, 2980) sought to prepare quinolylacetic acid by carboxylation of 2-quinolylmethyl-lithium, but obtained mainly (X), the product of addition of phenyl-lithium to quinaldine.

The carbinols (IV and V; R = Me, R′ = H) would be of special interest to us. Low yields of impure compounds resulted from reactions between equivalent quantities of *o*-aminoacetophenone and 2-pyridylmethyl- and 2-quinolylmethyl-lithium. Using excess of the former reagent we have, however, isolated mediocre yields of (IV; R = Me, R′ = H), but have not yet been successful in the quinoline series.

2-Thienyl-lithium reacted readily with *o*-aminoacetophenone to give 1-*o*-aminophenyl-1-2′-thienylethanol (XI).

Experiments with the carbinols mentioned above will be described later.

EXPERIMENTAL

M. p.s are uncorrected. All lithium reagents were prepared under an atmosphere of nitrogen. The ether and benzene used were dried over sodium. All ethereal extracts were dried over anhydrous sodium sulphate.

Reactions with 2- *and* 3-*Pyridyl-lithium.*

1-o-*Aminophenyl*-1-2′-*pyridylethanol*.—*n*-Butyl bromide (14·35 g.) in dry ether (40 c.c.) was added dropwise during ½ hour to lithium wire (1·80 g.) in dry ether (80 c.c.) at −20° to −15°, with stirring. The mixture was stirred for 1 hour at 0—10° and then filtered through glass wool. The solution was cooled to −60°, and then 2-bromopyridine (14·96 g.) in ether (30 c.c.) was added during 15 minutes and the whole was stirred for 5 minutes more. *o*-Aminoacetophenone (6·43 g.) in ether (50 c.c.) was added during 20 minutes, after which the temperature was allowed to rise to −15° and the stirring continued for 1 hour. The yellow complex was decomposed with water (50 c.c.), and the mixture shaken with aqueous ammonia and extracted with ether. Concentration of the extract gave yellow needles of the carbinol (3·70 g.), m. p. 95—96°, and subsequently a second crop (0·60 g.), m. p. 92—93°, was obtained.

If after decomposition with water the reaction mixture was extracted with ether, without being washed with ammonia, removal of the ether provided a viscous brown oil. Dissolution of this in methanol, followed by addition of ether, gave yellow crystals. Several crystallisations from methanol–ether gave yellow prisms of 1-o-*aminophenyl*-1-2′-*pyridylethanol hydrobromide*, m. p. 172—173° (Found: C, 52·9; H, 4·2; N, 8·7. $C_{13}H_{15}ON_2Br$ requires C, 52·9; H, 5·1; N, 9·5%).

1-(2-*Amino*-5-*chlorophenyl*)-1-2′-*pyridylethanol*.—5-Chloro-2-aminoacetophenone (8·1 g.) in ether (50 c.c.) was added during 20 minutes to 2-pyridyl-lithium (from 14·96 g. of 2-bromopyridine) at −60°. After being stirred for 1 hour at −15° the complex was decomposed with water, and the mixture was shaken with aqueous ammonia and extracted with ether. Concentration of the extract gave the *carbinol* (6·35 g.), m. p. 108—113°. It crystallised from ethanol as pale yellow needles (5·4 g.), m. p. 115—116° (Found: C, 62·9; H, 5·3. $C_{13}H_{13}ON_2Cl$ requires C, 62·8; H, 5·3%). In one experiment, despite the treatment with ammonia, the carbinol separated as its hydrobromide and the free base was liberated by grinding this with aqueous ammonia (*d* 0·88).

1-o-*Aminophenyl*-1-2′-*pyridylpropanol.*—By the method described for 1-*o*-aminophenyl-1-2′-pyridylethanol, *o*-aminopropiophenone (7·2 g.) gave the corresponding carbinol (5·7 g.) as yellow prisms, m. p. 82—84°. 1-o-*Aminophenyl*-1-2′-*pyridylpropanol* formed colourless prisms, m. p. 83—84°, from ether (Found : C, 73·4; H, 7·05. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·1%).

1-o-*Aminophenyl*-1-3′-*pyridylethanol.*—The same method was employed as for the 2-pyridyl-compound. 3-Pyridyl-lithium when treated with *o*-aminoacetophenone (6·43 g.) yielded yellow prisms of the product (3·60 g.), m. p. 143—145°, together with a second crop (0·65 g.), m. p. 134—142°. The pure *carbinol* (3·55 g.) separated from benzene as yellow prisms, m. p. 147—148° (Found : C, 73·9; H, 6·5. $C_{13}H_{14}ON_2$ requires C, 72·8; H, 6·6%).

1-o-*Aminophenyl*-1-3′-*pyridylpropanol.*—3-Pyridyl-lithium was treated with *o*-aminopropiophenone (7·2 g.) in the usual way. Decomposition of the reaction mixture with water gave a yellow precipitate (6·3 g.), m. p. 179—180°, which was collected and dried. 1-o-*Aminophenyl*-1-3′-*pyridylpropanol* crystallised from aqueous methanol in clusters of light brown needles, m. p. 185—186° (Found : C, 73·0; H, 7·5%).

1-o-*Aminophenyl*-1-4′-*pyridylethanol.*—4-*o*-Aminobenzoylpyridine (0·82 g.) in ether (100 c.c.) was added in one portion to a stirred Grignard reagent [from magnesium (0·46 g.), methyl iodide (2·75 g.), and ether (34 c.c.)] and the resulting red suspension was heated and stirred under reflux for 1$\frac{1}{2}$ hours. Decomposition with ice and ammonium chloride, followed by ether-extraction, provided the substantially pure product (0·62 g.). The *carbinol* crystallised from ether as colourless needles, m. p. 199—200° (Found : C, 72·4; H, 6·6%).

1-o-*Aminophenyl*-1-4′-*pyridylpropanol.*—Prepared by the above method, with ethyl-magnesium iodide, this *compound* formed fawn-coloured needles (from alcohol), m. p. 181—182° (Found : C, 73·2; H, 6·4; N, 12·2%).

Reactions with 2-*Pyridyl- and* 2-*Quinolyl-methyl-lithium.*

The efficiency of the procedure used in preparing these reagents was occasionally checked by titration of the intermediate phenyl-lithium (*J. Amer. Chem. Soc.*, 1932, **54**, 1957), which was formed in yields varying only slightly from 87·5%.

o-*Aminophenyl*-p-*methoxyphenyl*-2-*pyridylmethylcarbinol.*—(i) Bromobenzene (18·01 g.) in ether (40 c.c.) was added during $\frac{1}{2}$ hour to lithium (1·58 g.) with stirring, and the mixture was then refluxed gently with continued stirring for $\frac{3}{4}$ hour. 2-Picoline (9·53 g.) was added, and the dark red mixture stirred for 1 hour at room temperature. The ketone (23·28 g.) in benzene (50 c.c.) and ether (50 c.c.) was then added during $\frac{1}{4}$ hour, and the orange suspension was stirred for 4 hours at room temperature and 1 hour under reflux. After cooling, it was decomposed with water (150 c.c.) and set aside for 12 hours. The crystalline product was collected (8·25 g.; m. p. 148—149°), washed with a little ether, and dried. Recrystallisation from methanol gave soft cream-coloured needles, m. p. 153—154°. Variable amounts of the original ketone could be recovered from the ether–benzene layer by concentration and long storage.

(ii) In a similar procedure, except that the 1 hour of refluxing was omitted, the ketone (14·73 g.) in benzene (50 c.c.) reacted with 2-pyridylmethyl-lithium (2 equivs.; from 2·00 g. of lithium in 100 c.c. of ether) to give a crude product (13·1 g.; m. p. 143—145°) which provided 10·7 g. (51·5%) of pure material, m. p. 151—152°, after crystallisation. Small amounts of crude product could be obtained by concentration of the reaction solution.

Under the same conditions the use of 3 equivalents of the reagent gave 78% of product.

(iii) Solutions of 2-amino-4′-methoxybenzophenone (22·84 g.) in benzene (80 c.c.) and of phenyl-lithium (from 1·55 g. of lithium) in ether were prepared. To a preparation of 2-pyridyl-methyl-lithium (from 1·55 g. of lithium) in ether was added one-half of the ketone solution (causing the red solution to become yellow-brown), and after $\frac{1}{4}$ hour one-half of the phenyl-lithium solution (which restored the original red colour). Subsequently, ketone and phenyl-lithium were added alternately, in the amounts, after the times, and with the effect listed : $\frac{1}{4}$, $\frac{1}{2}$ hour, yellow red; $\frac{1}{4}$, 1 hour, red; $\frac{1}{8}$, $\frac{1}{2}$ hour, yellow red; $\frac{1}{8}$, $\frac{1}{2}$ hour, purple red; $\frac{1}{16}$, $\frac{1}{4}$ hour, orange red; $\frac{1}{16}$, $\frac{1}{4}$ hour, purple red; $\frac{1}{32}$, $\frac{1}{4}$ hour, orange red; $\frac{1}{32}$, $\frac{1}{4}$ hour, purple red; remainder of the ketone, $\frac{1}{4}$ hour, orange red. After 2$\frac{1}{2}$ hours' stirring at room temperature, and working up in the usual way, the mixture gave 16·0 g. of the carbinol, m. p. 149—150°.

Similar yields were obtained in three successive experiments, but subsequent runs failed.

1-o-*Aminophenyl*-1-*phenyl*-2-2′-*pyridylethanol.*—2-Aminobenzophenone (10·6 g.) in benzene (50 c.c.) was added to 2-pyridylmethyl-lithium (2 equivs.; from 1·64 g. of lithium in 100 c.c. of ether) during 10 minutes, and the mixture was then stirred for 4 hours at room temperature. Worked up as usual the reaction gave a crude product (10·65 g.; m. p. 140—142°) which was crystallised from ethanol, needles of the carbinol (9·3 g., 59·6%), m. p. 161—162°, being obtained. The ether–benzene layer was concentrated to a small volume and benzene was then added; after some days, more (0·88 g.) of the crude carbinol, m. p. 146—150°, separated.

1-o-*Aminophenyl*-2-2′-*pyridyl*-1-p-*tolylethanol*.—2-Amino-4′-methylbenzophenone (6·36 g.; Kippenberg, *Ber.*, 1897, **30**, 1133) in benzene (30 c.c.) was added to 2-pyridylmethyl-lithium (2 equivs.; from 0·93 g. of lithium) in ether (100 c.c.), and the orange-red suspension was then stirred for 4 hours. Concentration of the ether–benzene solution, obtained after decomposition in the usual way, at 95° and under vacuum gave a red glass which after dissolution in ethanol (20 c.c.) provided a crystallne solid (5·57 g.), m. p. 112—113°. The *carbinol* separated from aqueous ethanol as cream-coloured needles, m. p. 115—116° (Found: C, 79·7; H, 6·6. $C_{20}H_{20}ON_2$ requires C. 78·9; H, 6·6%).

1-(2-*Amino*-5-*chlorophenyl*)-1-*phenyl*-2-2′-*pyridylethanol*.—By the method just described 2-amino-5-chlorobenzophenone (7·13 g.; Angel, *J.*, 1912, **101**, 516) gave a yellow brown product (4·51 g.), m. p. 139—143°. The *carbinol* crystallised from ethanol in yellow prisms (3·77 g.), m. p. 143—144° (Found: C, 69·9; H, 5·4. $C_{19}H_{17}ON_2Cl$ requires C, 70·3; H, 5·3%).

1-o-*Aminophenyl*-1-*phenyl*-2-2′-*quinolylethanol*.—This compound was prepared by the method described more fully below for its methoxyphenyl analogue. 2-Aminobenzophenone (12·0 g.) with 2 equivalents of 2-quinolylmethyl-lithium gave a product (15·8 g.), m. p. 130—131°. White needles of the carbinol (7·8 g., 38·3%), m. p. 158—159°, were obtained from methanol.

1-o-*Aminophenyl*-1-p-*methoxyphenyl*-2-2′-*quinolylethanol*.—(i) 2-Amino-4′-methoxybenzophenone (18·56 g.) in benzene (50 c.c.) was added to 2-quinolylmethyl-lithium (1 equiv.; from 1·26 g. of lithium in 100 c.c. of ether) during ½ hour. After 5 hours' stirring at room temperature the red solution was decomposed with water (100 c.c.), and the carbinol (13·18 g.), m. p. 147—148°, was collected. White feathery crystals (9·3 g., 30·9%), m. p. 154—155°, were obtained by digestion with ethanol (700 c.c.).

(ii) With 2 equivalents of the lithium reagent (from 1·45 g. of lithium in 100 c.c. of ether) the ketone (10·68 g.) gave by the same method 48·1% of purified product.

1-(2-*Amino*-5-*chlorophenyl*)-1-*phenyl*-2-2′-*quinolylethanol*.—2-Amino-5-chlorobenzophenone (6·75 g.) in benzene (30 c.c.) was added during 10 minutes to 2-quinolylmethyl-lithium (from 0·90 g. of lithium in 100 c.c. of ether). The mixture was stirred for 4 hours and decomposed with water (100 c.c.). The ether–benzene layer was concentrated to a small volume (15 c.c.), alcohol (10 c.c.) was added, and the yellow crystals (5·83 g.), m. p. 130—143°, which separated on cooling, were collected. Pale yellow needles of the *carbinol* (3·60 g.), m. p. 154—155°, were obtained from ethanol (Found: C, 73·4; H, 5·4. $C_{23}H_{19}ON_2Cl$ requires C, 73·7; H, 5·1%).

1-o-*Aminophenyl*-2-2′-*quinolyl*-1-p-*tolylethanol*.—2-Amino-4′-methylbenzophenone (5·26 g.) in benzene (30 c.c.) was added to 2-quinolylmethyl-lithium (from 0·77 g. of lithium in 100 c.c. of ether), and the mixture was stirred for 4 hours. After the addition of water (100 c.c.) the grey precipitate was collected (3·95 g.; m. p. 125—127°). Yellow needles of the *carbinol*, m. p. 137—138°, separated from alcohol (Found: C, 81·6; H, 6·55. $C_{24}H_{22}ON_2$ requires C, 81·3; H, 6·3%).

1-o-*Aminophenyl*-3-2′-*pyridylpropan*-2-*ol*.—*o*-Aminoacetophenone (4·73 g.) in benzene (30 c.c.) was added during 10 minutes to 2-pyridylmethyl-lithium (2 equivs.; from 1·08 g. of lithium in 80 c.c. of ether). The mixture was stirred for 1 hour and decomposed with water (100 c.c.). Extraction with ether and removal of this solvent gave a viscous red oil (7·46 g.) which was distilled at 0·4—0·5 mm. The fraction, b. p. 154—184° (4·23 g.), was crystallised from ether–light petroleum (b. p. 60—80°), giving pale yellow needles (2·10 g.; m. p. 67—70°). Two further crystallisations from the same solvent mixture gave colourless prisms of the *carbinol*, m. p. 84—85° (Found: C, 73·6; H, 7·3. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·1%).

1-o-*Aminophenyl*-1-2′-*thienylethanol*.—Redistilled thiophen (8·86 g.) in ether (10 c.c.) was added to phenyl-lithium (from 1·5 g. of lithium in 100 c.c. of ether), and the mixture was refluxed for 2 hours. *o*-Aminoacetophenone (7·18 g.) in ether (50 c.c.) was added dropwise during ¼ hour at −15° and the brown solution was then stirred for 1 hour at room temperature. After decomposition of the complex with water (50 c.c.) the mixture was extracted with ether. This ethereal extract was washed with water and shaken with hydrochloric acid (600 c.c. of 15%), and the acid solution was then washed with a small amount of ether. Basification of the acid layer with aqueous ammonia followed by ether-extraction provided a dark brown oil (9·15 g.) which was distilled at 1·0—1·5 mm. The oil provided several fractions boiling over a very wide range, but those collected (5·32 g. in all) from 142° to 182° slowly crystallised. They were combined and recrystallised from ether–light petroleum (b. p. 60—80°), giving a pale yellow product (3·67 g.), m. p. 62—64°. The pure *carbinol* formed colourless prisms, m. p. 66—67°, from the same solvent mixture (Found: C, 65·4; H, 6·3. $C_{12}H_{13}ONS$ requires C, 65·7; H, 6·0%).

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